COMPARISON OF LITHIUM AND SODIUM VALPROATE COMBINATION THERAPY WITH SODIUM VALPROATE MONOTHERAPY IN EUTHYMIC BIPOLAR PATIENTS

Dissertation submitted for partial fulfillment
of the rules and regulations

DOCTOR OF MEDICINE

BRANCH - XVIII (PSYCHIATRY)

THE TAMILNADU DR.MGR MEDICAL UNIVERSITY,

CHENNAI,

TAMIL NADU

MAY 2018

CERTIFICATE

This is to certify that the dissertation titled, **"COMPARISON OF LITHIUM AND SODIUM VALPROATE COMBINATION THERAPY WITH SODIUM VALPROATE MONOTHERAPY IN EUTHYMIC BIPOLAR PATIENTS"** is the bonafide work of **Dr. ASHWINI MUTHUSAMY,** submitted in partial fulfillment of the requirements for M.D. Branch-XVIII [Psychiatry] examination of The Tamilnadu Dr. M.G.R. Medical University, to be held in May 2018.

The Director,
Institute of mental health
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CERTIFICATE OF GUIDE

This is to certify that the dissertation titled, **"COMPARISON OF LITHIUM AND SODIUM VALPROATE COMBINATION THERAPY WITH SODIUM VALPROATE MONOTHERAPY IN EUTHYMIC BIPOLAR PATIENTS"** is the bonafide work of **Dr. ASHWINI MUTHUSAMY,** done under my guidance submitted in partial fulfillment of the requirements for M.D. Branch-XVIII [Psychiatry] examination of The Tamilnadu Dr. M.G.R. Medical University, to be held in May 2018.

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DECLARATION

I, **Dr. ASHWINI MUTHUSAMY,** solemnly declare that the dissertation titled, **"COMPARISON OF LITHIUM AND SODIUM VALPROATE COMBINATION THERAPY WITH SODIUM VALPROATE MONOTHERAPY IN EUTHYMIC BIPOLAR PATIENTS"** is a bonafide work done by me at the Institute of Mental Health, Chennai, during the period from March 2017 – July 2017 under the guidance and supervision of **Dr. SHANTHI NAMBI M.D., F.I.P.S,** Professor of psychiatry, Madras Medical College.

The dissertation is submitted to the The Tamilnadu Dr. M.G.R. Medical University towards partial fulfillment of requirement for M.D. Branch XVIII [Psychiatry] examination to be held in May 2018.

Place :

Date : **Dr. ASHWINI MUTHUSAMY**

ACKNOWLEDGEMENTS

I am grateful to Professor **Dr. NARAYANABABU, M.D., D.C.H.,** Dean, Madras Medical College, Chennai, for permitting me to do this study.

I am deeply indebted to my teacher professor **Dr. SHANTHI NAMBI,** M.D., F.I.P.S., Director, Institute of Mental Health, Chennai for her kind words of encouragement and immeasurable support to conduct and complete this study.

I must profusely thank my guide Associate professor **Dr. VENKATESH MATHAN KUMAR,** M.D., for providing me with direction, guidance and encouragement throughout, without which this study would have been a futile attempt.

I thank my associate professors **Dr. V. Sabitha** M.D., **Dr. Poornachandrika** M.D. and **Dr. Jegadeesan,** M.D. for their support and encouragement.

I am very grateful to my co-guide Asst. Professor **Dr. Jaikumar,** M.D., for his valuable support and guidance for the study.

I am very grateful to Assistant Professor **Dr. Vanishree, M.D., D.P.M.,** for steering me throughout the study and for being a moral support throughout.

My immense thanks to Assistant Professors **Dr.Neelakandan** M.D., **Dr. Hemapriya**, M.D. and **Dr.Bevin** M.D., for their constant support.

I wish to express my sincere gratitude to all the Assistant Professors of our department for their valuable support and guidance.

I am thankful to all the staff of Institute of Mental Health for their help and compassionate attitude.

I thank my friends at the institute for their immense help and support throughout the course period.

I am indebted to The Almighty, my parents, my sister and my friends for being a continuous support throughout.

Finally, but most importantly, I would like to thank all my patients and attenders who cooperated and participated in this study.

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CERTIFICATE OF APPROVAL

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Dear Dr.Ashwini.M. ,

The Institutional Ethics Committee has considered your request and approved your study titled **"COMPARISON OF LITHIUM AND SODIUM VALPROATE COMBINATION THERAPY WITH SODIUM VALPROATE MONOTHERAPY IN EUTHYMIC BIPOLAR PATIENTS " - NO.23012017 (IV).**

The following members of Ethics Committee were present in the meeting hold on **31.01.2017** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.M.K.Muralidharan,MS.,M.Ch.,Dean, MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.B.Vasanthi,MD., Prof.of Pharmacology.,MMC,Ch-3	: Member
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6.Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch	: Member
7.Prof.S.Mayilvahanan,MD,Director, Inst. of Int.Med,MMC, Ch-3	: Member
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9.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
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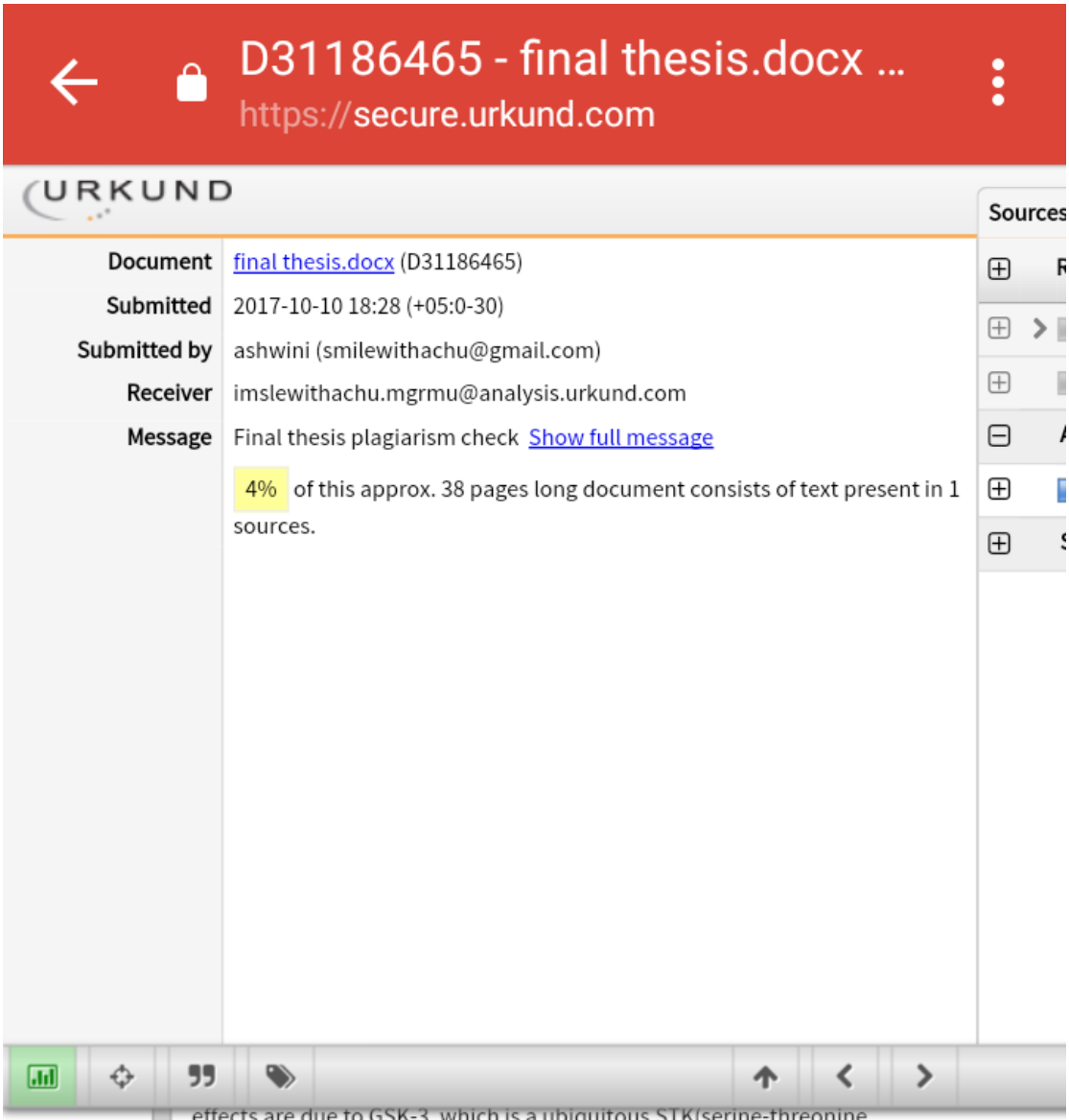


effects are due to GSK-3, which is a ubiquitous STK(serine-threonine kinase). By binding to the magnesium-sensitive site of the enzyme, lithium inhibits GSK-3 directly and indirectly by enhancing phosphorylation of STK at certain serine residues. 2.

Apart from GSK-3, lithium inhibits phosphomonoesterases (

inositol polyphosphate1-phosphatase, inositol monophosphate phosphatase, fructose 1,6-bisphosphatase, and bisphosphate nucleotidase

and phosphoglucomutase. Inhibition of these enzymes plays a small role. 3.

The

phosphatidylinositol 3-kinase (PI3K)/Akt pathway mediates lithium's indirect inhibitory effects of lithium GSK-3 by elevating its

CONTENTS

ABBREVATIONS

BPAD	-	Bipolar affective disorder
ICD-10	-	International Statistical Classification of Diseases and Related Health, problems-Tenth Revision-10
GAF	-	Global assessement of functioning scale
WHOQOL-BREF	-	World Health Organisation Quality of Life-brief version
HAM-D	-	Hamilton depression rating scale
YMRS	-	Young's mania rating scale
FAB	-	Frontal Assessment Battery
TMT-A	-	Trail making test-part A
TMT-B	-	Trail making test-part B
DF	-	Digit Forward
DB	-	Digit Backward
BALANCE	-	Bipolar Affective disorder: Lithium/ANti-Convulsant Evaluation
FDA	-	Food and Drug Administration
HDAC	-	Histone Deacetylase

GSK-3	-	Glycogen Synthase Kinase-3
ESK	-	Extracellular Signal Related Kinase
CGC	-	Cerebellar Granule Cells
CSF	-	Cerebrospinal Fluid
MSCs	-	Mesenchymal Stem Cells
ER	-	Endoplasmic Reticulum
HSPC	-	Hematopoietic Stem Progenitor Cells

INTRODUCTION

Bipolar Affective Disorder being a complex episodic illness with high suicidality and comorbidity requires an equally complex pharmacological therapy [1]. There has been evidence accumulating since the 1990s that the recovery achieved in bipolar illness is not complete, especially in terms of psychosocial difficulties as well as cognitive deficits [2]. Also, sudden treatment discontinuation can cause serious effects [3] that is improper treatment can lead to more number of episodes and increased hospitalizations [4]. All these factors thus impose significant psychological as well as socioeconomic burden on patients and also care givers [2]. This impact of illness in turn affects longevity, relationships, career, and self-esteem [4].Many authors state that quality of life in Bipolar affective disorder can be affected even by the depressive symptoms [5].

Lithium was the gold standard treatment as maintenance in Bipolar affective disorder for more than forty years by reducing relapse and suicide risk, but has been found to be not helpful for all the patients due to its narrow therapeutic index and adverse effects, thus leading to suboptimal adherence [6-9]. This lead to search for alternative treatments and one such widely used drug is sodium valproate, which is effective for its antimanic and also relapse prevention properties [10,11] . Valproate being one of the most utilised mood stabilisers, has very little evidence for its effectiveness [1].

Since many do not seem to respond to monotherapy, drug combinations are often recommended inspite of the presence of very little evidence [12,13]. Lithium and valproate combination is the most recommended after the failure of monotherapy that is commonly used as first-line treatment [6]. If this combination is found to have synergistic pharmacological effects it may prove better than the monotherapy and could even be used as a first-line therapy [14-16], but the comparison between this combination and monotherapy has been rarely done in the past [2]. BALANCE (Bipolar Affective disorder: Lithium/ANti-Convulsant Evaluation), a randomised trial was an important large study done that established that valproate semisodium plus lithium is better than valproate monotherapy [17].

Some Studies have reported that lithium alone in acute manic states can shorten the remission time markedly and also reduce other neuroleptics dosage [18]. On the other hand, studies also state that the combination therapy of lithium and valproate is even more effective in reducing the time to remission and the dosage of other drugs[19]. Since, literature is sparse with respect to this, this study has been done to compare the effectiveness of this combination therapy with valproate monotherapy.

Such patients have neurocognitive deficits when compared to healthy controls [20,21] even in the asymptomatic or euthymic period once symptoms have resolved [22-24]. Even after about twenty years of scientific work, the nature, extent and pattern of the cognitive deficits is still being the focus of debate as well as research, as they remain uncertain [25]. The number of

episodes, number of hospital admissions and the duration of illness in particular were found to be negatively related to cognitive functions [22,23,26].

Regarding cognition, while valproate was seen to affect attention in BPAD patients [27], lithium was found to affect psychomotor functioning, speed, attention and memory, in few studies [28,29]. In few others, cognition was found to remain unaffected even after chronic administration of lithium [30,31]. On the other hand literature also addresses the neuroprotective effects of lithium, along with valproate [32-34]. Lithium and valproic acid have been found to have neuroprotective properties both in vivo and in vitro. Synergistic neuroprotective effects of this combination treatment have been seen against glutamate induced excitotoxicity in cultured neurons of the brain, by potentiating inhibition of glycogen-synthase-kinase-3 (GSK-3) activity [35]. Still few other studies state that pharmacological agents have no effect on cognition [36].

Since, the literature is inconsistent on the effects of lithium and valproate on cognitive functions in BPAD patients, this study also tries to compare neurocognition between the combination and valproate monotherapy, to see if the synergism brings about neuroprotection as stated in an article that dealt with in vitro settings [37].

Thus, in the background of such controversial and scarce literature, this study aims to assess the effectiveness of the combination of lithium and sodium valproate therapy in euthymic bipolar patients by comparing it with sodium valproate monotherapy in terms of quality of life, functioning and cognition.

REVIEW OF LITERATURE

TREATMENT OF BIPOLAR DISORDER

According to Judd and Akiskal, Bipolar Spectrum Disorders can have prevalence even till 8% in the general population [38]. Treatment includes resolution of acute episodes as well as in the maintenance-prevention of relapses [39].

Acute phase is easily managed with antipsychotics and benzodiazepines. Mood stabilizers, on the other hand are used in the maintenance phase to prevent relapses or recurrences. They thus maintain elevated and depressive moods of the patient. Antidepressants with mood stabilizers are used to treat bipolar depression. Some antipsychotics are used to treat manic episodes due to their thymoleptic properties in the acute phase as mood stabilizers take time to act [48].

Bipolar disorder can occur as depression, mania, mixed episodes (both mania and depression) as well as hypomania and can cause extreme shifting in the thinking, mood, behavior and energy of the patient. Because of these mood swings sometimes there is difficulty in diagnosis and differentiation, and being a life-long illness in many this can affect one's career, interpersonal relationships, self-esteem and longevity [2]. Rapid cycling with or without psychotic features are associated with treatment resistance and adherence [4,6]. This disorder recovers after treatment of long duration, and while most have rapid cycling, lifelong, there is also an increased tendency to recur. This relapse

is prevented by long term treatment and discontinuing treatment suddenly can cause adverse effecs [40]. As a result of all these, bipolar disorder can cause marked socioeconomic burden as well as psychosocial impairment on patients as well as their care givers. When left untreated, there can be more number of episodes and more hospitalizations[2].

Relapse prevention is important as:

(i) more episodes affect cognition negatively [41]

(ii) Relapses have been associated with structural changes in brain [42]

(iii) Patients with more episodes had a poorer quality of life [43]

Mood stabilizers, mostly lithium have been found to have changed the long term prognosis of the patients [44]. They showed their superiority over placebo in acute episodes as well as in relapse prevention [45]. Geddes et al, in their study found that there was a mean relapse rate of 40% in lithium treated bipolar patients [46]. Altamura et al found that patients treated with valproate alone had a higher relapse rate of 67.15% , thus proving that lithium was more effective than valproate in preventing relapses [47].

LITHIUM:

Lithium follows hydrogen and helium on the periodic table, making it the third simplest element (atomic number 3, atomic weight 6.94) and the first solid element [48].

PHARMACOLOGICAL ACTIONS:

Lithium is rapidly absorbed, with serum concentrations peaking in 1 to 1.5 hours- standard preparations and in 4 to 4.5 hours-controlled-release forms. Lithium neither has protein-binding properties nor any metabolites. It is excreted through kidneys, sweat and faeces. Some amount of lithium is reabsorbed from the proximal tubules, so that renal lithium clearance is about one-fifth of creatinine clearance. The elimination half-life of lithium is about 18 to 24 hours generally. Elderly people generally need lower doses to reach a given serum concentration. Thyroid and renal concentrations exceed serum level, whereas red blood cell, spinal fluid, and brain concentrations do not. Lithium enters and leaves the CNS slowly, which explains why acute overdoses with relatively high blood levels are sometimes well tolerated and why clinical manifestations of chronic intoxications often persist long after blood levels have decreased substantially[49].

Mania

Lithium is an established, first line, antimanic drug with effectiveness greater than placebo. It is one of the FDA approved drugs for treating manic episodes, and continues to be among the first choices. Its onset of action is relatively slow, with improvement occurring over 1 to 3 weeks.

Depression

Lithium is not FDA approved for bipolar depression treatment unlike quetiapine, lurasidone or olanzapine/fluoxetine combination) Breakthrough

depression during lithium maintenance calls to check for hypothyroidism induced by lithium, irregular drug intake, or substance abuse. Factors that are associated with inadequate or reduced response to lithium maintenance are multiple previous episodes, poor functioning between episodes, comorbid personality disorder or substance use.

Lithium was used initially in 1850 for treating gout and in as a sedative cum antiepileptic in 1900 but were found to be less successful. Cealius Aurelianus, in the 5th century, suggested lithium for mania [49]. In 1949, John F. Cade in his article presented that lithium use was associated with improvement in manic patients and not in those with dementia praecox but this made minimal impact at that time [50]. As the drug was cheap, it was not patented also [51]. FDA approved its use in treatment of mania in 1969 and a prophylactic treatment for bipolar affective disorder in 1971.

In India, lithium use started in various places. Professor N. N. Wig at PGI, Chandigarh used lithium in 1968 itself even when it was not being marketed [52]. In Tamilnadu, Madurai Medical College, in 1974, started a lithium-clinic under Professor Venkoba Rao.

According to some studies, even children tolerated and responded with lithium well, no side effect was severe that warranted its stoppage, also no depression or exacerbations of episodes were seen during lithium prophylaxis in these children, and no renal impairment was seen [53-56].

Main Side effects of long term lithium treatment

Renal function

Lithium, eliminated mostly through kidneys, during acute intoxication can impair their function [57-59].

Effect on glomerular filtration rate (GFR)

GFR that was estimated by creatinine clearance was found to be normal in patients on long term lithium maintenance as low creatinine clearance was neither correlated with serum lithium levels or the duration of treatment.

Effect on tubular function

Polyuria alongwith thirst occurs as lithium interferes with antidiuretic hormone in distal tubules of the kidney producing a syndrome like nephrogenic diabetes insipidus, which is totally reversible with withdrawal of lithium. This is correlated closely with serum lithium levels.

Renal morphology

Though some studies focused on long term changes in the kidney morphology following chronic lithium treatment, many others have been found to be non-specific as these could be induced by other drugs the patient might be receiving or other forms of chronic nephropathy [59,60]. Till 1991, Khandelwal states that there was no report of any patient who died due to renal insufficiency induced by lithium. Similarily, Aiff et al, 2014, stated that low dose lithium may even prevent kidney damage [61]. But contrary to these,

Markowitz et al, 2000, McKnight et al, 2012, and many others reported that patients taking lithium for long durations had kidney function impairments, sometimes even necessitating dialysis. This makes regular serum creatinine estimations mandatory, once lithium is started.[62,63]

Pre-lithium screening, especially in developing countries like ours must be done in order to avoid various other expensive investigations. This includes blood urea, serum creatinine, serum electrolytes, 24-hr urine volume, TFT (thyroid function tests), weight and ECG [59].

Serum lithium levels is an indirect lithium concentration measure at activity and toxicity sites. Inadequate levels can result in failure of treatment, whereas increased concentrations result in toxicity. Lithium level recommended as the therapeutic range is 0.8-1.2 mEq/L. 0.6-1.0 mEq/L is recommended for maintenance. Many studies reported effective prophylaxis even on lower serum lithium levels [64]. Goodnick and Fieve (1985), in their 3 yr old study found that there was no difference in inter-episode functioning or in the side effects in two groups of bipolar patients maintaining on high and low lithium levels [65]. Though lithium use has increased significantly, the limitation seems to be the lack of facilities to measure serum lithium. Kuruvilla (1977) suggested that serum for lithium estimation could be sent by post as these levels remain stable over time [66].

Single loading doses of lithium can also cause more abortions and gastrointestinal side effects. Renal damage in single daily dose regimen has

been reported in some studies [66-69]. They found that single daily doses were associated with low 24 hour urine volume and fewer changes in kidney biopsies than multiple doses.

REASONS TO DISCONTINUE LITHIUM:

1) One of the important reasons to discontinue treatment is side effects which occur in more than 40% of cases [70]. Tremors and memory problems are the most common reasons for men to stop lithium, while women stop it mainly because of polyuria and weight gain.

2) Another important reason for patients to stop lithium is the very success of lithium in reducing their upswings in mood which they miss while on lithium prophylaxis. Patients believe that lithium interferes with their creativity and productivity [71].

3) In many poorly supervised patients discontinuation usually occurs when patient is on the verge of hypomania .

4) Other reasons contributing to poor compliance and discontinuation are intercurrent physical illnesses, pregnancy, poor social support, and a chaotic home environment.

5) Not having good psychotherapeutic support and psychoeducation programmes for the patient and his family may also decrease patient's adherence to the treatment plan [72].

Predictors of response to lithium

1) Favourable predictors are compliance to treatment, response in the past, good premorbid personality, affective illness, appropriate serum levels.

2) Another favourable predictor was found to be family history of bipolar disorder in some studies [73, 74] while others failed to show such association[75, 76].

3) Joyce and Paykel in 1989 suggested that bipolar II disorder may have a poorer response with lithium than bipolar I [77] .

4) High expressed emotion was found to be linked with a poor response to prophylactic lithium [78, 79].

Age of onset, age of start of lithium, gender were not found to influence or have any effect [80]. Altogether, there have been no consistent reports or studies to predict lithium response.

Lithium and pregnancy

Lithium use in pregnancy has been found to be associated with neonatal deaths and congenital defects like Patent Ductus Arteriosus, Coarctation of aorta, single umbilical artery, valvular atresias, etc [81]. Thus, it should be avoided in the first trimester of pregnancy. The termination of lithium itself may carry a high risk of relapse. Lithium may also be found in infants, as it is excreted in breast milk but Schou et al (1976) found no effects of lithium on

physical or mental development, in children on lithium born without any malformations[80].

LITHIUM AND SUBSTANCE USE:

Sarah Sportiche et al in 2016, found that substance, mainly alcohol use disorder and mixed episodes were associated with lower or no response to treatment with lithium [82]. This could have been due to the non-adherence to treartment usually seen in patients with substance use disorder [83,84], but other studies saw that even those bipolar patients with comorbid substance use disorder, with good adherence to treatment were not found to be associated with an improved response. These patients are found to have a young age of onset [85, 86], high self-harm risk, severe symptoms, frequent episodes [87, 88] and rapid cycling and mixed episodes [89]. In recent animal studies, lithium and alcohol were found to have opposite effects on the behavioural circadian rhythms [90]. Several studies suggest that lithium is not as effective as valproate for patients with mixed episodes [91, 92]. Another response predictor in several studies was family history of Bipolar disorder [93].

In a study by Hayes et al, which has supposedly the longest follow-up in direct comparisons of mood stabilizers, treatment failure rate was more for valproate (apart from olanzapine and quetiapine), as compared to treatment with lithium. This held good even when there were failures after first 3 months (even after patient was stabilized suggesting that lithium monotherapy is better than any other mood stabilizer used. This study also mentions that

though lithium superiority can be due to its close monitoring, it was found here that patients on lithium had fewer visits 40. Because of the side effects, lithium may be and is often avoided, but valproate, (as well as olanzapine or quetiapine) monotherapy was found to fail faster, only resulting in additive side effects by multiple psychotropic drugs [94].

SODIUM VALPROATE:

One of the forms of valproate, a simple chain branched chain carboxylic acid, sodium valproate represents one of the first-generation mood stabilizing anticonvulsants. It is FDA approved for monotherapy or adjunctive therapy of simple and complex partial seizures, and absence seizures; migraine prophylaxis and treatment of acute manic episodes in bipolar disorder. Its use in bipolar disorder was first reported by O. Lambert in France.

PHARMACOKINETICS:

It is rapidly absorbed with peak plasma levels attained 3-4 hours after oral administration. Its plasma half life is 10-16 hours, generally. Valproate is highly bound to albumin. At serum levels less than 45-50mcg/mL, these binding sites are unsaturated leading to less or no unbound valproate which is the pharmacologically active one that crosses the blood-brain barrier. Valproate is metabolized primarily by hepatic glucuronidation [48].

The first placebo-controlled studies by Harrison.G. Pope in 1991, and Charles L Bowden in 1994 were responsible for valproate receiving FDA indication for acute mania. Post hoc analyses of the Bowden study suggests

that, although there was no difference in the response rate for patients with euphoric mania, patients with depressive symptoms (i.e.,dysphoric mania) or a cumulative lifetime episode burden of greater than four prior depressive episodes or 11 prior manic episodes responded poorly to lithium. Furthermore, four distinct manic subtypes (anxious-depressed, psychotic, classic, and irritable) based on pretreatment symptom cluster analyses confirmed that the classic manic subtype responded similarly to divalproex and lithium, but the irritable manic subtype responded significantly better to divalproex than lithium or placebo [95].

Calabrese et al, in their study where they evaluated the spectrum of valproate's efficacy in 78 rapid-cycling bipolar patients of which 30 received valproate monotherapy and the remaining, either lithium or an antidepressant or carbamazepine etc. in combination, found that valproate exerts marked antimanic and antianxiety action but only mild to moderate antidepressant effects [96].

Though, lithium used to be the only mood stabilizer widely used, and remains the first choice of drug to prevent relapses in bipolar disorder, it was also observed that around 20% to 40% of patients do not respond to lithium adequately. Valproate, an anticonvulsant drug has been seen to be effective when used in acute episodes of mania and is also frequently used as maintenance treatment. Whenever efficacy of a drug as well as its acceptability as long-term treatment is considered, the adverse effects should also be taken into account. Calabrese et al in their study found results consistent with many

others that the most common side effects of valproate were gastrointestinal effects, lethargy, tremors, hair thinning followed by weight gain, sedation, hepatotoxicity, rashes etc [96]. A Cochrane review 2009 Update was done to determine valproate maintenance as well as continuation efficacy, in terms of preventing manic, depressive or mixed episodes and also in terms of functioning and general health of patients, to review the numbers of dropouts and their reasons, and thus the acceptability, and to study valproate adverse effects. Particapants were chosen from the following databases: The Cochrane Library, MEDLINE, EMBASE and PsycINFO. It was found that there was not at all any difference in efficacy between lithium and valproate. Valproate use was associated with lesser dropouts when compared to placebo or lithium. Nevertheless, lithium plus valproate combination therapy was even more likely to prevent relapse than valproate monotherapy. Lithium was also found to be more associated with adverse events like diarrhoea, polyuria etc whereas valproate was associated with increased sedation. Thus it was concluded that the efficacy of valproate in chronic treatment of bipolar disorder has limited evidence and thus the tolerability and acceptability should be considered by clinicians as well as patients, when choosing between lithium, valproate or their combination [97]

Valproate, whether used as monotherapy or in combination has surpassed lithium as the primary mood stabilizer in treating patients with bipolar disorder. Bowden et al did a narrative review wherein they tried to describe the the tolerability and efficacy of valproate in bipolar disorders, and

also saw the reasons for favorable or unfavorable outcomes. Higher valproate serum levels, that is above 110 ng/ml, were found to be associated with higher reports of sedation, weight gain and decrease in platelet count. On the one hand, valproate was found to be associated with increased occurrence of (PCOS) polycystic ovarian syndrome, while on the other hand it was also found to decrease total cholesterol levels, especially in those with cholesterol baseline elevations [95].

Valproate is the first choice of treatment in mania[97] as its Initial effects by are quicker than lithium [98] because of its faster onset of action, and is also equivalent to antipsychotics (haloperidol or olanzapine) [99–101].

Factors associated with response or non-response to valproate

1) Mixed episodes in bipolar disorder were found to be more responsive to valproate (divalproex) when compared to lithium [102].

2) Irritability was found to be associated with greater response to valproate (divalproex) than lithium, in bipolar disorder as well as others like personality disorders, schizophrenia etc. [103].

3) Those with past history of poor lithium response were shown to respond better to divalproex [98].

4) More mania or depression episodes (>8) especially >2 depressive episodes, were found to respond better with divalproex than lithium [104].

5) Atypical manic states, secondary to substance, other neurological disorders, later onset age were found to respond to valproate than lithium [105].

6) Patients with predominant feature as hyperactivity responded to both divalproex and lithium as compared to placebo, with no difference between the two, according to a systemic study. Also it was found that psychotic or depressive features in the manic episodes, when present, showed no improvement with divalproex or lithium when compared to placebo [104].

Kessing et al found that the overall rate of hospitalizations was more for patients on valproate as opposed to lithium after a year, mostly for those patients with an index depressive episode. They thus concluded that treatment with lithium seemed to be superior to treatment with valproate in terms of functioning [1].

CONCEPT OF DOUBLE MOOD STABILISERS

Lithium and sodium valproate combination therapy is found to be more effective than either monotherapy in many [106]. A number of studies have been conducted in China to compare the combination therapy with monotherapy. Liu et al, in their study, compared the efficacy of this combination therapy with lithium monotherapy and found that the former was more effective than the latter [19]. Xu et al, 2007 found that relapse rates in bipolar patients were markedly lower in those on the above combination rather

than the individual monotherapies [107]. They also reported that this combination was particularly useful in the rapid cyclers. Evaluation by evidence-based medicine was also done. Jin et al, 2011, in their meta-analysis, included six studies where lithium and valproate combination was compared with lithium monotherapy and the former was found to be associated with greater improvement in symptoms and lesser rates of remission [108].

Kumar et al reports that a combination of lithium, valproate and an antipsychotic, the triple drug regimen is the treatment in refractory bipolar disorder [4].

COMBINATION OF SODIUM VALPROATE AND LITHIUM

In a maintenance study comparing lithium plus valproate versus lithium alone, the combination was more effective than lithium alone; however, the adverse event profile was higher with the combination treatment. In the largest practical clinical trial (using a randomized open design), Geddes and colleagues found clear superiority of lithium compared to valproate, with the combination marginally better than lithium alone [46].

This study identified brain activity changes following lithium and valproate treatment in healthy volunteers. Decreased Blood Oxygen Level Dependent (BOLD) signal change in the lithium group was noted in the working memory task, while in the valproate group, it was in the spatial attention task. Both valproate and lithium had a reduced BOLD signal in the verbal task, compared to the placebo [109].

EFFECT OF INDIVIDUAL AND COMBINATION THERAPIES ON QUALITY OF LIFE AND FUNCTIONING

Quality of life in bipolar patients could be caused by the disorder per se, somatic complaints, substance use or side effects of medications. As lithium therapy allows better cooperation from the patient's side, the risk of adverse effects and other complications are reduced and thereby, the quality of life of the patients is improved. Here again if patients had a negative attitude to lithium or did not have a complete response or on the other hand, were on the verge of hypomania with lithium, they terminated the therapy. Vieta (2005) reported that educating patients about symptom identification and maintenance therapy improve lithium response and adherence, decreasing disease recurrences as well as hospitalizations, thereby improving the quality of life [110]. Dogan and Sabanciogullari (2003) also reported the same after a 3 month observational study [111]. Montes et al 2008 found depressive symptoms to negatively impact the patients' quality of life [112]. Chand et al. (2004) reported from their study, which involved bipolar patients on lithium and other anticonvulsants, and healthy controls, that the lithium patients' quality of life was no different from the latter, which they attributed to fewer side effects [113].

BALANCE study has found that the quality of life of bipolar patients on the combination of lithium and sodium valproate is better than those on the valproate monotherapy alone, and comparable to those on lithium, though none of the differences were statistically significant [17].

COGNITION IN BIPOLAR DISORDER

After two decades of scientific work the nature of the cognitive impairments is still the focus of research and debate. The extent and pattern of cognitive impairment in euthymic patients remain uncertain [114].

A meta-analysis of the studies revealed widespread cognitive deficits in patients with schizophrenia and affective disorders in speed of information processing, cognitive functioning, encoding and retrieval, rule discovery, response generation and inhibition [115].

Two kinds of pathological processes are involved in cognition impairment in bipolar disorder:

1) pruning, excitotoxicity or increased apoptotic activity –normal processes occurring excessively

2) decreased neurogenesis, progenitor cell generation senescence-trophic processes failure

Impairment of cognition in the following domains-verbal learning, verbal memory, attention and executive functions are regarded as a bipolar disorder feature because these persist even in the periods of remission. However, in these patients the cognitive impairments could also be induced by mood-stabilizers, the first line drugs used. Evaluations of motor speed reaction, memory and attention functioning, creativity and associative productivity represent a vital step for the bipolar patient monitoring, due to the effect of

anticonvulsants over these variables. The functional prognosis of the patients, their ability to cope with the social and professional duties and also their quality of life depend on the monitoring of symptoms and on reducing the factors having a negative impact on the cognitive functions, in significant proportions [116]. Vasile et al in his study, which involved cognition evaluation among mood stabilizers found that-

(i) Lithium was associated with reduced fluency, low motor performance as well as memory and verbal learning impairments, but were also reversible.

(ii) Valproate and carbamazepine were found to be associated with slowing of memory and reaction time and minor learning deficits.

(iii) Topiramate was associated with word-finding difficulties, bradykinesia, attentional and retrieval difficulties.

(iv) Oxcarbazepine and lamotrigine were found to have a favorable outcome, while gabapentin results were inconclusive and needs further study [117]

Many areas of cognition are impaired in the acute phases of bipolar illness persist even in the euthymic periods. Number of hospitalisations, number of episodes (particularly manic), chronicity and psychotic symptoms are the factors reported to negatively influence cognitive functioning in type I bipolar disorder, especially memory, attention and abstraction [26]. Impairment in cognitive functioning, especially memory disturbances, can in turn affect functional

outcome of patients with bipolar disorder, negatively [20]. Here again, another factor that might have a negative impact on psychosocial functioning and neuropsychological impairment are subsyndromal symptoms [118, 119].

Thompson et al studied a large sample of prospectively verified well-characterised bipolar disorder patients who were euthymic, with the following neuropsychological tests- the Trail Making Test- A, Vigil test, and Digit Symbol Substitution Test from the Wechsler Adult Intelligence Scale – Revised (WAIS–R) for *psychomotor performance*, Stroop Test, Trail Making Test-B, the Tower of London task from the Cambridge Neuropsychological Test Automated Battery (CANTAB), the Controlled Oral Word Association Test, the Digits Backward (sub-test from the WAIS–R), Abstract Designs Self-Ordered Pointing Task (SOPT;)- a computerised version, and the CANTAB for *Attention* and *executive function*; the Digit Forward (sub-test from the WAIS–R) and the CANTAB Spatial Span Spatial Working Memory test for *Immediate memory*; and the CANTAB Pattern Recognition Memory and Spatial Recognition Memory tasks, CANTAB Simultaneous and Delayed Matching to Sample, CANTAB Paired Associates Learning test and the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964) for *declarative memory (visual and verbal)* Cognitive domains like executive functions and attention, spatial memory, verbal and visuospatial memory were found to be affected in these patients. As basal salivary cortisol showed no difference between controls and patients, cognitive impairments were proved to not be due to hypercortisolism.

It was also seen that the dysfunction was evident even after controlling for residual mood symptoms effects [120].

EFFECT OF INDIVIDUAL AND COMBINATION THERAPIES ON COGNITION AND MECHANISMS INVOLVED:

The mood stabilizers lithium and valproic acid are traditionally used to treat BPAD, a severe mental illness arising from complex interactions between genes and environment that drive deficits in cellular plasticity and resiliency. The therapeutic potential of these drugs in other central nervous system diseases is also gaining support. This article reviews the various mechanisms of action of lithium and valproic acid gleaned from cellular and animal models of neurologic, neurodegenerative, and neuropsychiatric disorders.

Lithium and Sodium valproate induce the expression and transcription of angiogenic, neurotrophic, and neuroprotective proteins, by their action on glycogen synthase kinase-3 (GSK-3) and histone deacetylases (HDCs) respectively. Also these two drugs act on oxidative stress pathways, cell survival signaling cascades, and protein quality control mechanisms. Co-treatment of lithium and valproate has been found to cause neuroprotection and increase stem cell migration and homing. Preclinical findings show that the neuroprotection offered by these drugs facilitate angiogenesis, anti-inflammation, blood-brain barrier integrity, neurogenesis, etc. Although both these drugs have been used to treat Bipolar Disorder, the underlying mechanisms still remain elusive. Many factors like the dysregulation of

pathways of signaling and expression of genes, loss of synaptic plasticity, reduced cellular resilience, decreased density of brain cells and abnormalities in neuroanatomical functions and structure are believed to be involved I the etiology of bipolar disorder, although the exact etiology remains less understood [121]. These are counteracted by these 2 drugs in the following ways, while noting that in the biologic processes affected by lithium and valproic acid, there are similarities and differences according to Gupta et al, 2012 [122]:

MECHANISMS OF ACTION:

1) Glycogen Synthase Kinase-3 (GSK-3) for lithium and histone deacetylases (HDACs) for Valproate:-

The properties of inhibition of GSK-3 and HDAC by lithium and valproate, respectively are necessary for the numerous molecular mechanisms' facilitation help in the therapeutic use.

Lithium and GSK-3

1. The primary facilitator of the mood stabilizing and neuroprotective effects are due to GSK-3, which is a ubiquitous STK (serine-threonine kinase) By binding to the magnesium-sensitive site of the enzyme, lithium inhibits GSK-3 directly and indirectly by enhancing phosphorylation of STK at certain serine residues.

2. Apart from GSK-3, lithium inhibits phosphomonoesterases (inositol polyphosphate1-phosphatase, inositol monophosphate phosphatase, fructose 1,6-bisphosphatase, and bisphosphate nucleotidase and phosphoglucomutase. Inhibition of these enzymes plays a small role.

3. The phosphatidylinositol 3-kinase (PI3K)/Akt pathway mediates lithium's indirect inhibitory effects of lithium GSK-3 by elevating its phosphorylation at Ser21.

Valproate and HDACs

1. Valproate also has strong anti-manic effects, but is not as effective against depressive episodes as lithium. Efficacy of valproate in bipolar disorder results from increased gama-aminobutyric acid (GABA) neurotransmission and inhibition of enzymes that metabolise GABA-succinate semialdehyde reductase, succinate semialdehyde dehydrogenase and GABA transaminase but primarily by inhibition of HDACs as a result of which it promotes a more transcriptionally active chromatin structure.

2. Bowden et al in their review also reports that even valproate inhibits glycogen synthase kinase; thus activates signal-regulated kinase (ERK)

2) Neurotrophic and Angiogenic Factors Modulation

During neural development and synaptic plasticity, neurotrophic and angiogenic factors play vital roles.

Lithium and valproate particularly augment 3 of these which are

a) BDNF (Brain-Derived Neurotrophic Factor)

b) GDNF (Glial-cell Derived Neurotrophic Factor)

c) VEGF (Vascular Endothelial Growth Factor)

a) BDNF-

The neuroprotective effects of Valproate and lithium are facilitated, in part, by inducing BDNF and activating its receptor, that signals through the TrkB (Tyrosine-kinase B) receptor to augment cortical development, neurogenesis, synaptic plasticity and neuronal survival. Hashimoto et al, 2002, for example, proved that pre-treatment with lithium or BDNF protected primary cortical neurons from undergoing glutamate excitotoxicity [123]. Chronic lithium treatment is neuroprotective even in hypoxia, by elevating BDNF levels [124].

b) GDNF-

Lithium increased GDNF levels in striatum, hippocampus and prefrontal cortex contributing to the antidepressant-like effects and protected against endoplasmic reticulum (ER) and mitochondrial stress-mediated apoptosis.

Valproate, on the other hand, has been shown to protect against lipopolysaccharide (LPS) induced neurotoxicity, due to its inhibition of pro-inflammatory factors in primary neuronal-glial cocultures from rat midbrain.

c) VEGF-

VEGF is an important angiogenic factor that promotes angiogenesis to enhance trophic support by the formation of new blood vessels from existing ones.

While treatment with lithium increased VEGF levels in both endothelial cells and astrocytes, valproate enhanced VEGF induced angiogenesis in cultured endothelial cells. This upregulation of VEGF is mediated by the transcription factor hypoxia inducible factor-1a (HIF-1a)

3. Factors Affecting Apoptotic Signaling: Bcl-2, p53, Bax, Caspase Signaling, and HSP70

Apoptosis (programmed cell death) involves many biochemical signaling cascades. Both the drugs lithium and valproate were found to increase mRNA expression of antiapoptotic protein Bcl-2 in rat frontal cortex; valproate was shown to upregulate Bcl-2 mRNA in spinal cord in a mouse model of ALS.

Lithium increased the expression of Bcl-2, decreased the expression of the proapoptotic proteins p53 and Bax, and suppressed the mitochondrial release of glutamate-induced cytochrome c in glutamate excitotoxicity challenged primary brain neuronal cultures.

Lithium, in addition, was found to attenuate NMDA-receptor phosphorylation, and thus modulate the NMDA receptor activity and excitotoxicity at the synapses [124].

Heat shock proteins (HSPs)

HSPs are molecular chaperones regulating folding of proteins as well as refolding of misfolded proteins, thus promoting cell survival. It has been found that HSP70, exerts neuroprotection against apoptosis by antagonizing factors that induce apoptosis, by inhibiting nuclear factor-kB (NF-kB) activation and by preventing release of mitochondrial cytochrome c and activation of caspase. HSP70 is modulated by a transcription factor (heat shock factor-1:HSF-1) regulated negatively by phosphorylation by GSK-3b. Thus, the neuroprotection offered by lithium are associated with increase in the HSF-1 and therefore, elevations in HSP70 protein expression in the ischemic brain [122].

According to an experiment of cells challenged with (mitochondrial complex I inhibitor) rotenone, valproate's neuroprotective effects involves HSP70 and might be associated with reductions in cytochrome c release and cleavage of caspases. HSP70 was again involved in neuroprotection by valproate, by inhibition of HDACs, against glutamate excitotoxicity in rat cortical neuronal cultures [122].

4. Cell Survival Signaling Cascades

The neuroprotective mechanisms of valproate and lithium also involve survival signaling cascades, like the, Wnt/b-catenin pathway, and MAP kinase-

kinase (MEK)/extracellular-signal regulated kinase (ERK) pathway, PI3K/Akt pathway.

a. The PI3K/Akt Pathway

As seen earlier, BDNF induction is an essential and early step in the neuroprotection offered by lithium against glutamate excitotoxicity. BDNF's neurotrophic action is involved in activation of PI3K/Akt and MEK/ERK pathways induced by lithium. It was found that in rat cerebellar granule cells (CGCs) cultured, lithium normalized glutamate-induced Akt inactivation by activating PI3K and thus increasing Akt phosphorylation . After activation, Akt mediates antiapoptotic Bcl-2 protein, procaspase-9 etc.

Valproate, although HDAC inhibitor, via BDNF-mediated activation of the PI3K/Akt pathway is reported to cause slight increases in Akt and GSK-3b phosphorylation under certain in-vitro conditions. Thus valproate is implicated in both the PI3K/Akt and MEK/ERK pathways' activation.

b. The Wnt/b-Catenin Pathway

Wnt pathway, by synapse formation and controlling axon remodeling, regulates neuronal connectivity. Lithium treatment activates Wnt/b-catenin pathway and contributes to adult hippocampal cell proliferation and also increased b-catenin levels in vitro as well as in vivo , through its GSK-3 activity.

Valproate alters Wnt signaling in both animal and human cells. Interestingly, Valproate by upregulating Wnt/b-catenin pathway and subsequently causing imbalance in the oxidative homeostasis in early pregnancy might facilitate susceptibility to autism. But in aging CGCs valproate co-treatment was seen to enhance neuroprotective effects induced by lithium against excitotoxicity, through the transcriptional activity dependent on b-catenin. Also valproate, by increasing b-catenin expression, altered angiogenic processes studied in umbilical vein endothelial human cells [122].

c. The MEK/ERK Pathway

ERK regulates downstream effectors like NF-kB, in turn inhibiting GSK-3b and activating CREB, which is a transcription factor as well as a common target of both MEK/ERK and PI3K/Akt pathways. CREB, when activated through phosphorylation, promotes the expression of BDNF and Bcl-2 and lithium after ischemia, was seen to enhance ERK phosphorylation, thus activating CREB. But again, lithium's effects may be cell type–specific, on this pathway, as it was found to have contrasting effects on MEK/ERK pathway in different cell types.

Valproate activates this pathway, increases ERK-regulated genes (Bcl-2) expression, and is seen to promote cell survival and neural growth in cultured human neuroblastoma cells. Valproate prevented attenuation of ERK activation, leading to CREB phosphorylation, and thus the expression of Bcl-2

and BDNF in the frontal cortex, in a sleep deprived animal model-manic-like behavior [122].

5. Oxidative Stress Pathways

Oxidative stress can cause ensuing damage of the cellular lipids, proteins, DNA and organelles, and can activate stress-sensitive signaling processes. This mechanism is associated with manic episodes. Markers of oxidative metabolism-thiobarbituric acid reactive substances, catalase, superoxide dismutase (SOD) were seen to be elevated in manic patients not on drugs, when compared to both lithium treated manic patients and healthy controls, thus concluding that lithium reduces oxidative stress, thereby reducing cellular damage[123].

6. Protein Quality Control Mechanisms

a. Induction of the Ubiquitin-Proteasome System and Autophagy.

These are two major quality control mechanisms for clearance of abnormal protein accumulation. Autophagy, a potential neuroprotective mechanism, has been found to be induced by lithium through inhibiting inositol monophosphatase and inositol transporters. Lithium facilitated mutant huntingtin and a-synuclein clearance and also of prion proteins that were protease-resistant in prion-infected cells , and thus found to be protective in Amyotrophic Lateral Sclerosis model mice, with this autophagy-inducing property [125]. Valproate by decreasing IP3 levels also induces autophagy [122].

b. Glucose Regulated Protein (GRP) 78 Upregulation

Endoplasmic Reticulum (ER) being the major site for protein synthesis, trafficking and folding is highly sensitive to stress. Lithium and valproate were shown to protect ER from stress by upregulating HSP70 and the 78-kDa GRP78, which binding to calcium, helps in protein folding, involves in stress-induced autophagy, thereby protecting cells from misfolded proteins in the ER [122].

7. miRNAs regulation by Lithium and Valproate

miRNAs, the non–protein-coding RNAs, function in mRNA degradation and translational repression by binding and can thus lead to silencing of genes, thus playing a regulatory role in nervous system.

After chronic treatment with lithium or valproate, regulation of miR-34a and GRM7 (Glutamate Metabotropic Receptor-7), in vivo has been found. Muscarinic acetylcholine receptor alterations are also associated with BPAD and lithium normalizes these deficits partly by M1-receptor-ERK pathway signaling enhancement, as studied in the animal model. This was attributable to downregulation of an earlier recognized miRNA that was lithium responsive [122].

8. Augmented Protective Effects by Lithium and Valproate Cotreatment

The diverse neuroprotective mechanisms of lithium and valproate range from neurotrophic factors (BDNF) augmentation, anti-apoptotic factors' (such

as Bcl-2) facilitation to the survival-signaling cascades (enhancing the PI3K/Akt signaling pathway) regulation. These are primarily mediated by GSK-3 and HDAC inhibition. This combination of lithium and valproate provides synergistic effects in terms of neuroprotection in the following ways:

Enhanced Neuroprotection by Cotreatment

Though both lithium and valproate, individually, cannot exert their neuroprotective factors by the above mechanisms in aging or older CGCs, Leng and colleagues studied that their combination completely blocked glutamate induced excitotoxicity in the aging CGCs. Thus in older CGCs only combination therapy was found to be neuroprotective, while monotherapy was even somewhat detrimental [126].

Bone marrow derived Mesenchymal stem cells (MSCs) have been studied to cause beneficial effects in animal models of neurodegenerative diseases. MSCs are limited by their their poor homing and migratory abilities, in treatment, as otherwise these release trophic factors and hasten regeneration and repair, on reaching the injured brain site. This homing and migratory ability of transplanted MSCs could therefore be expected to improve their therapeutic efficacy. MSC migration toward injured brain areas occurs by the interaction between SDF-1a (stromal cell–derived factor 1a) and CXC-chemokine receptor 4 (CXCR4), whose expression is enhanced by valproate. Also, MSC migration depends on the Wnt signaling pathway which gets

activated by GSK-3b inhibition, that is enhanced by lithium. Hence, lithium and valproate combination additively enhance MSC migration[125].

Hematopoietic stem cells (HSCs), that promote angiogenesis and neuroplastic effects in ischaemic brains, when transplanted, have been found to transdifferentiate into glial cells as well as neurons in the brain. Transplantation of HSCs has been shown to promote angiogenesis and enhance neuroplastic effects in the ischemic brain. Valproate and lithium combination therapy was found to preserve the HSPCs' immature cell-phenotype in haematopoietic differentiation, by delaying differentiation of HSPCs (hematopoietic stem progenitor cells) and increasing the cell survival potential.[125]

EFFECT OF VALPROATE ON COGNITION:

Valproate was found to be associated with slowing of memory and reaction time and minor learning deficits but are found to be reversible [126].

EFFECT OF LITHIUM ON COGNITION:

For bipolar disorder and schizoaffective disorders, lithium is the standard management with a known toxicity profile [127]. Lithium was also found to result in better learning and memory by protecting irradiated hippocampal neurons, in these mice, from apoptosis[128].

Alexsandra et al, in their study compared cognition among healthy controls, bipolar patients who were excellent responders to lithium and those

who were non-excellent responders to lithium, and found that excellent lithium responders did not differ much from those of control thus concluding that lithium treatment is associated with a preservation of cognition[129].

Neuroimaging in humans also supports that lithium exerts neuroprotective action, in addition to animal studies. For example, lithium when used for four weeks as treatment in bipolar patients, was shown to increase grey-matter content of the brain, in a study that involved 3-D magnetic resonance imaging [130], thereby concluding that this effect probably occurred as a result of neurotrophic effects. Studies also show that bipolar patients on long-term lithium therapy have fewer changes on brain imaging compared to patients with at least 2 years of illness who received lithium for less than 3 months. Those not treated with lithium had smaller left hippocampal volumes than controls [131].

In another study involving left prefrontal N-acetyl aspartate (NAA) level measurement, performed using magnetic resonance spectroscopy at 1.5 Tesla, it was found that the group not on lithium had lower prefrontal NAA levels than the lithium-treated or control groups [132]. Kessing et al. showed that patients on lithium were more likely, to develop dementia than general population; but, for those continuing to take lithium, the rates fell to those of the general population [133]. This finding is unclear and needs further study as people with mood disorders have an increased risk of developing cognitive impairment more so, dementia, compared with the general population, and so this could be a proxy of the disease-effects. Those taking anticonvulsants had

results, otherwise. Yet another follow-up study found that continued treatment with lithium was associated with a decreased rate of dementia in bipolar patients, in contrast to continued treatment with antidepressants, anticonvulsants, or antipsychotics [134]. Minor negative effects on cognition were found in a meta-analysis of lithium [135].

In a study investigating amnestic mild cognitive impairment in patients on long-term lithium treatment, significant decrease in CSF concentrations of P-tau was found.

Lithium was used as a neuroprotectant, in an early-phase study, that was presented in an abstract form at the 2007 American Society for Therapeutic Radiology and Oncology [136], and again updated at the 2008 annual meet of the Society of Neuro-Oncology [137].

Having said this, lithium when used to treat patients with mild Alzheimer's disease, in yet another placebo-controlled single blind study, for 10 weeks, there were no significant benefits on either CSF concentrations of disease-related biomarkers or cognitive performance[138], contrary to the above findings.

It has been seen that people taking lithium mostly have no complaints about the effects on mental processes. However, mild cognitive effects can occur, although it becomes difficult to determine whether these are due to the drug itself, due to the resolution of manic episode, presence of mild depression or hypothyroidism, or also due to other drugs. Cognitive complaints may

include reduced reactivity, loss of emotional tone, lack of spontaneity, patchy memory impairment etc. Lithium due to its negative effects on memory, information processing speed and memory, it was suggested that the risk in driving with lithium may be increased, but no such accidents were reported [139].

Bipolar Disorder is associated with impairments in attention, working memory, information-processing speed, and executive dysfunction. Neuroimaging in bipolar affective disorder have shown ventricles to be enlarged, raised white matter hyperintensities around the ventricles (WMHs) - suggestive of vascular disease and decreased speed of information processing seen in normal aging, as well as low fractional anisotropy (FA) -a measure of white matter tract integrity while integrating neurocognition with these findings. One study found that reductions in gray matter in the temporal lobe were associated with impaired cognition and number of episodes. [140]

A meta-analysis involving 12 studies with 276 subjects taking lithium for around 3.9 years, concluded that only few minor negative effects on cognition were observed. All these studies conclude the possibility that lithium may not provide cognitive enhancement, but may protect from cognitive deterioration over the long-term. Thus literature regarding effects of lithium on cognition is mixed. [135]

Cognitive impairment in bipolar disorder patients is not only restricted to the symptomatic phases but is also seen in the euthymic phase. This was

found out by observing differences in the brain's structure between bipolar patients and healthy individuals, as well as changes in patients, with time. Lithium is considered the gold standard, especially in long-term prophylactic treatment as it prevents new episodes, improves the disease course and reduces number of harmful outcomes.

Preclinical data show that lithium has a neuroprotective effect but there is only limited data on its effects in humans and even lesser on long-term application. Pfenning et al, 2005 in their study, compared cognition of healthy controls with bipolar patients on short term and long term lithium and found that patients and controls did not differ significantly in overall cognitive functioning and verbal learning, recall, and recognition; regardless of whether lithium had been part of the treatment [141]. Patients demonstrated worse early visual information processing than the healthy controls. Spectroscopic and volumetric data that accompanied, suggest cell loss in patients not treated with lithium that may be counterbalanced by long-term lithium treatment [142].

Neurocognitive impairment can be considered as a "state or trait". There are numerous studies on neurocognitive performances in euthymia of mood disorder patients [143]. According to Ferrier & Thompson, 2002, even a euthymic person, between episodes of mood disorder, can exhibit trait dysfunction. In depressed or manic subjects, neurocognitive deficits can result from state as well as trait contributions. They can be affected and influenced by medications used as treatment [144].

Jaramillo et al assessed cognition using neuropsychological tests of memory, attention, and executive function on 60 subjects-20 euthymic patients on lithium, 20 without treatment and 20 healthy controls. Bipolar I patients, on a whole, performed worse on episodic verbal and visual-verbal memory, irrespective of medication status, compared to controls. No significant differences were found among the first two groups, suggesting that no deleterious effects on cognition were caused by the use of lithium. Thus, they concluded that the verbal memory deficits that occur in bipolar I disorder patients are not due to lithium, but due to the condition itself [145].

AIMS AND OBJECTIVES

Aim:

The aim of the study is

1. To compare the functioning of euthymic bipolar patients on lithium and sodium valproate combination therapy with those on sodium valproate monotherapy.

2. To compare the quality of life of euthymic bipolar patients on lithium and sodium valproate combination therapy with those on sodium valproate monotherapy.

3. To assess certain neurocognitive domains in euthymic bipolar patients on lithium and sodium valproate combination therapy and those on sodium valproate monotherapy and compare them.

NULL HYPOTHESIS:

1. There is no difference between the functioning of euthymic bipolar patients on the lithium and sodium valproate combination therapy and, those on sodium valproate monotherapy.

2. There is no difference in the quality of life of euthymic bipolar patients on the lithium and sodium valproate combination therapy, and those on sodium valproate monotherapy.

3. There is no difference in the cognitive domains tested between the euthymic bipolar patients on the lithium and sodium valproate combination therapy, and those on sodium valproate monotherapy.

MATERIALS AND METHODS-METHODOLOGY

ETHICAL CONSIDERATIONS:

An application was submitted to the ethics committee of Madras medical college under Dr.MGR medical university in the month of February 2016. Permission was given to conduct the research in Institute of mental health .The ethical committee approval obtained in March 2016 and document is enclosed in the appendix.

Need and purpose for the study, procedure, confidentiality of details, benefits due to study were all explained to the participants.

The study is a cross-sectional analytical study conducted at the Institute of Mental Health, Chennai. Consecutive patients attending outpatient department were screened for diagnosis of bipolar affective disorder according to ICD-10 criteria.

Selection Criteria:

GROUP 1:

Inclusion Criteria:

1. Patients with bipolar affective disorder diagnosed according to ICD-10.
2. Patients between 20-55 years of age.

3. Patients who have been euthymic for atleast 6 months- (HAM-D ≤8, YMRS≤6)

4. Patients who have given written consent to participate in the study, including attenders.

5. Patients who are on Sodium Valproate and Lithium as mood stabilizers for atleast 1 year.

6. Patients who have normal vision and hearing by history and clinical examination.

Exclusion Criteria:

1. Those with other mental disorders

2. Those with uncontrolled medical conditions

3. Those with neurological disorders

4. Those with learning difficulties

5. Those with past history of ECT

Group 2

Inclusion Criteria:

1. Patients who are diagnosed to have Bipolar Affective Disorder as per ICD-10.

2. Patients between 20-55 years of age.

3. Patients who have been euthymic for atleast 6 months(HAM-D ≤8, YMRS≤6)
4. Patients who have given written consent to participate in the study, including attenders.
5. Patients who are on Sodium Valproate as mood stabilizer for atleast 1 year.
6. Patients who have normal vision and hearing by history and clinical examination.

Exclusion Criteria:

1. Those with other mental disorders
2. Those with uncontrolled medical conditions
3. Those with neurological disorders
4. Those with learning difficulties
5. Those with past history of ECT

Euthymia was confirmed by 2 senior psychiatrists apart from the rater, ie YMRS≤6, and HAM-D≤8 [152].

TOOLS

1. Semi-structured proforma to collect sociodemographic data and clinical characteristics of group 1 and group 2
2. Global Assessment of Functioning Scale (GAF)
3. World Health Organisation Quality Of Life-BREF (WHOQOL-BREF)
4. Frontal Assessment Battery (FAB)
5. Stroop Word Colour Test
6. Trail-making Test-A (TMT-A)
7. Trail-making Test-B (TMT-B)
8. Digit Forward (DF)
9. Digit Backward (DB)

DESCRIPTION OF TOOLS:

1. **Socio-demographic data**

    a) Age in years

    b) Gender

    c) education

    d) occupation

    e) marital status

ILLNESS DETAILS:

    a) duration of illness

    b) total number of episodes

    c) total number of manic episodes after treatment

    d) total number of depressive episodes after treatment

    e) other medications

2. **Global Assessment Functioning (GAF) Scale**

It is a numerical scale used by clinicians to rate the occupational, social and psychological functioning of an individual, subjectively. Scores range from 100 (extremely high functioning) to 1 (severely impaired) in ranges (eg. 91-100, 81-90 etc.) This scale belongs to the DSM-IV version. The main advantage of this is the brevity [146].

3. **World Health Organization Quality Of Life Scale-Brief version (WHOQOL-BREF):**

It is a globally cross - culturally comparable quality of life evaluation instrument. It assesses the individual's perceptions in the context of their culture, value systems, personal goals, standards and concerns. It comprises 26 items, which measures 4 domains - physical health, psychological health , social relationships and environment. This tool has a good reliability (Cronbach alpha - 0.66 to 0.87) for each domain. Higher scores on each of the domains shows higher personal satisfication in that specific domain. The WHOQOL-BREF tool is a shorter version of the original instrument which is more convenient for use in large research studies or clinical trials [147].

4. **Frontal lobe Assessment Battery** [148]

The neuropsychological tool, Frontal Assessment Battery (FAB), was devised by Dubois et al. It is short and helps in assessing executive functions at the bedside. The FAB has of six subtests, covering widely the functions of frontal lobes. Each subset has a score from 0 to 3. The maximum score is 18. A score of 12 or below is considered abnormal. Higher scores indicate better performance. Time taken to administer the battery is about 10 minutes. The functions analysed are:

S.No	Functions tested	Tests
1.	Conceptualization	Similarities task
2.	Mental flexibity	Phonological fluency task
3.	Motor programming	Luria's motor series
4.	Sensitivity to interference	Conflicting instructions task
5.	Inhibitory control	Go-no-go task
6.	Environmental autonomy	Prehension behavior

1. Conceptualization:

In frontal lobe dysfunction, abstract reasoning is affected. Patient will not be able to make a similar abstract link between items tested.

2. Mental flexibility:

The non-routine functions that require cognitive strategies are disturbed in frontal lobe lesions. Fluency tasks require retrieval from semantic memory. Verbal fluency is reduced in frontal lobe dysfunctions. In this test, the individual tells from his memory the number of words possible with the given letter.

3. Motor programming:

Intact function of frontal lobe is required in tasks of temporal organization and carrying out successive actions. In Luria's motor series, such as "fist–palm–edge," the person needs to do the series in correct sequence without simplification like two gestures instead of three and perseveration.

4. Sensitivity to interference:

In tasks in where verbal commands contradict the sensory information, self regulation is required. When instructions are given to patient to act to the opposite of what they see, in frontal lobe dysfunction the patients could not refrain from sensory stimuli and fail to follow verbal command.

5. Inhibitory control:

It tests the ability of the person to withhold an inappropriate response. The go-no-go test assesses the ability of the individual to control the impulsiveness to act, that is to inhibit an act that was done to the same stimuli previously.

6. Environmental autonomy:

Patients with frontal lobe dysfunction, has a spontaneous tendency to adhere to the environment. They lack the inhibitory response of the prefrontal cortex on the act triggered by certain sensory stimulations.

5. TRAIL-MAKING TEST-A AND B (TMT-A & B):

This test, which is included in the Halstead Reitan Battery is a measure of visual searching, visual sequencing, perceptuomotor speed, the ability to make alternating conceptual shifts efficiently, and attention.

The Trail Making Test (TMT) consists of two parts. TMT requires subjects to connect 25 consecutively numbered circles in part A (1,2,3,4,….) and 25 numbered and lettered circles by shifting between the two sets in part B (1-A.2-B,3-C,4-D,….) as quickly as possible, and is very sensitive to cerebral dysfunction. Part A of the test measures psychomotor speed. The results of part B reflect the ability to shift strategy and assess executive function, visuospatial working memory and cognitive processing speed . Time is recorded in seconds.

The errors committed are not recorded, as every error is corrected by the examiner before proceeding, and thus the errors also contribute to increase in time taken to complete the test [149]

6. DIGIT SPAN FORWARDS:

This test is a part of Weschler-Adult Intelligence Scale (WAIS-) wherein digit sequences are presented beginning with a length of two digits and two trials are presented at each increasing list length. Testing ceases either when the subject fills in accurately reporting the trial at one length or when the maximal list length is reached, which is nine digits forwards.

Digits should be given at the rate of one per second in an even monotone without any variation in the pitch of the voice. Care should be taken not to follow a certain sequence while giving digits like only odd or only even numbers or consecutive numbers etc. This test assesses attention [150].

7. Digit span backwards:

This test is a part of Weschler-Adult Intelligence Scale (WAIS-) wherein digit sequences are presented beginning with a length of two digits and two trials are presented at each increasing list length. Testing ceases either when the subject fills in accurately reporting the trial at one length or when the maximal list length is reached, which is eight digits backwards.

Digits should be given at the rate of one per second in an even monotone without any variation in the pitch of the voice. Care should be taken not to follow a certain sequence while giving digits like only odd or only even numbers or consecutive numbers etc. This test is for assessing working memory [150].

8. STROOP TEST (ALEXANDER, BENSON AND STUSS, 1989):

This test measures the response inhibition ability. On a sheet, the names of colours “blue”, “green”, “red” and “yellow” are printed in capital letters. The colour of the print and the word printed might not match up. But occasionally both may correspond. The words are printed in 16 rows and 11 columns. The sheet will be placed in front of the individual to be tested. First the individual is asked to read the word and not the colour of the word in

column-wise as fast as possible. The examiner notes down the time taken in seconds to read all the 11 columns. Next, the individual is asked to name the colour in which the word is printed column wise. The examiner notes the time taken to name all the colours. The words were given in the mother tongue of the subject.

Stroop effect score = Time taken to name the colour – Time taken to read the words [151]

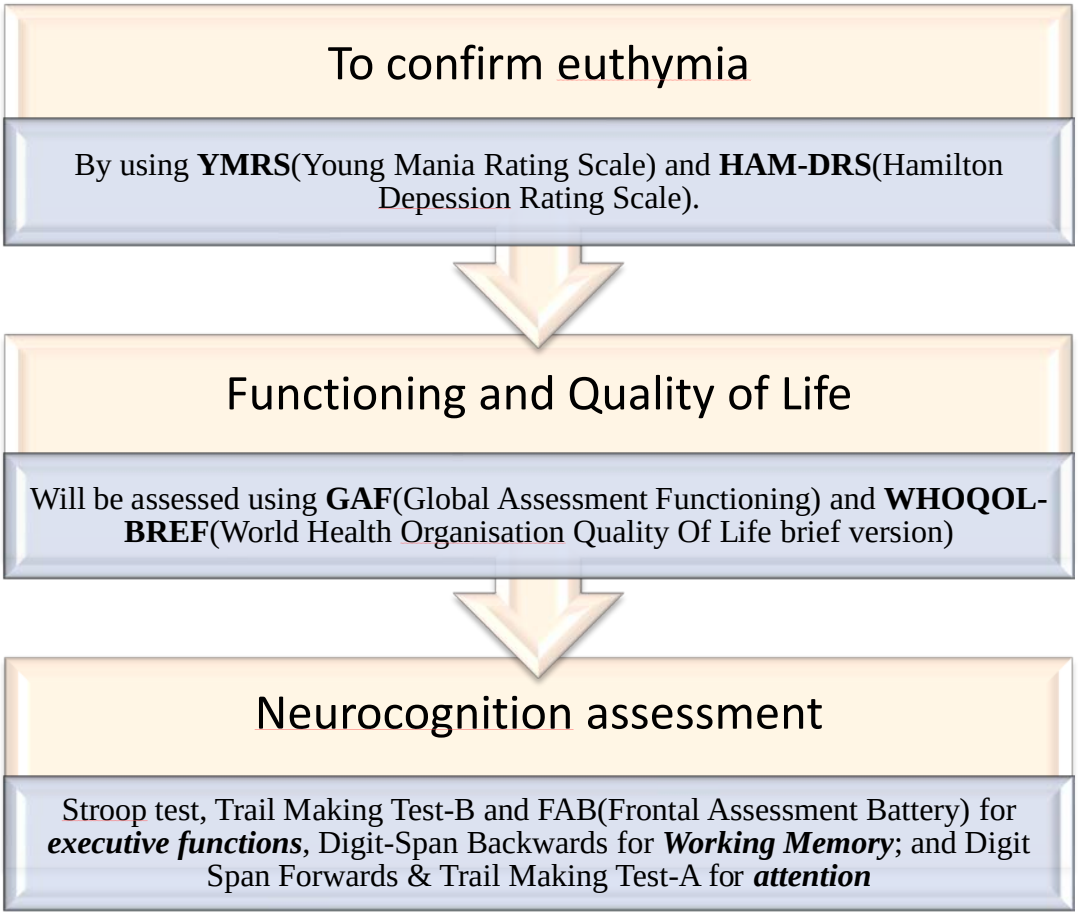
OPERATIONAL DESIGN:

This was a hospital based study, conducted at Institute of Mental Health, Madras Medical College, Chennai in a cross sectional analytical design, for a period of five months (March 2017-July 2017) Approval from the Institutional Ethical Committee, Madras Medical College was obtained. The sample was chosen from psychiatry outpatient department of Institute of Mental Health. Patients diagnosed as bipolar disorder as per ICD 10 who were on sodium valproate and lithium combination therapy, as mood stabilizers were chosen as group 1 and those diagnosed as bipolar disorder as per ICD 10 who were on sodium valproate monotherapy, as mood stabilizer were chosen as group 2. Both the groups were screened depending on the inclusion and exclusion criteria, and were included in the study.

The study subjects were explained about the nature of the study and consent was obtained. Socio demographic details as per proforma were collected from groups 1 and 2. Complete physical examination including

detailed Neurological evaluation was done. Subsequently, all subjects were given the scales and cognitive assessments as mentioned.

Tests were administered in a quiet room in a fixed pre-set order according to standard administration instructions. The time taken was about 1hr to 1hr and 30 minutes. Assessments were carried out in 1-2 sessions, each session not extending beyond 1 hour.



STATISTICAL DESIGN

Statistical design was formulated using the data collected as above.

SAMPLE SIZE CALCULATION:

This was done using G power software.

Analysis: A priori

Input : tail (s) - one

Effect size (d) - 0.8

Alpha error probability - 0.03

Power (1-beta probability) - 0.95

Allocation ratio (N_2 / N_1) – 1

Output : Sample size group 1 - 40

Sample size group 2 - 40

Total sample size - 80

Actual power – 0.951142

Statistics used:

Statistical analysis was done using the IBM SPSS version 20.

Group characteristics description and comparison was done using Chi-square test. Pearson correlation test was used to compare WHOQOL-

BREF domains with age, and Spearmann Rank correlation test to compare WHOQOL-BREF with gender, education and occupation.

Independent t test was used to compare the difference in mean scores on test performances between the combination group and the monotherapy group. Paired t tests were performed to compare the number of episodes of illness in both groups before and after the treatment with mood stabilizers.

RESULTS

TABLE-1: SOCIODEMOGRAPHIC DATA OF BOTH GROUPS:

		Groups				
		Combination drug (SVP & Li)-group 1		Single drug (SVP)-group 2		p value
		Count	Column N %	Count	Column N %	
Sex	Male	22	55.0%	20	50.0%	0.317
	Female	18	45.0%	20	50.0%	
Marital status	Married	22	55.0%	23	57.5%	0.114
	Single	12	30.0%	12	30.0%	
	Separated	4	10.0%	2	5.0%	
	Widow / widower	2	5%	3	7.5%	
Education group	Primary & secondary	37	92.5%	38	95.0%	0.251
	Degree / Diploma/PG	3	7.5%	2	5.0%	
Occupation group	Unemployed/ Homemaker	14	35.0%	17	42.5%	0.186
	Unskilled	14	35.0%	11	27.5%	
	Semi skilled/Skilled	12	30.0%	12	30.0%	

This table has the sociodemographic data of the patients of the 2 groups- sodium valproate and lithium combination therapy (group 1) and sodium valproate monotherapy (group 2)

In the first group, 55% were males and 45% were females, while in the second group, both males and females were 50%.

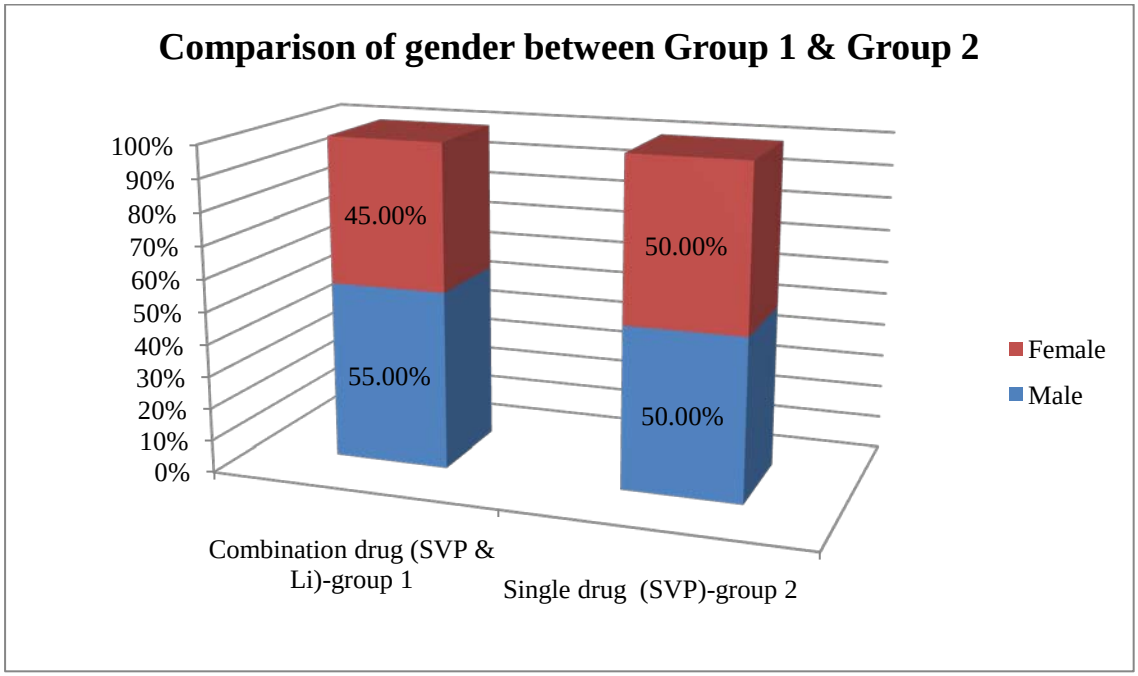
In the first group, 55% were married, 30% were single-unmarried, 10% were separated from their spouses, 5% were widows/widowers. In the second group, 57.5% were married (slightly more than the first group), 30% were single (similar to the first group), 5% were separated from their spouses (slightly lesser than the first group), 7.5% lost their spouses(slightly more than first group)

92.5% had completed primary or secondary education in group 1, while in group 2 it was 95%. 7.5% in group 1 had done diploma or had a degree or were a postgraduate, while in group 2 this comprised 5%.

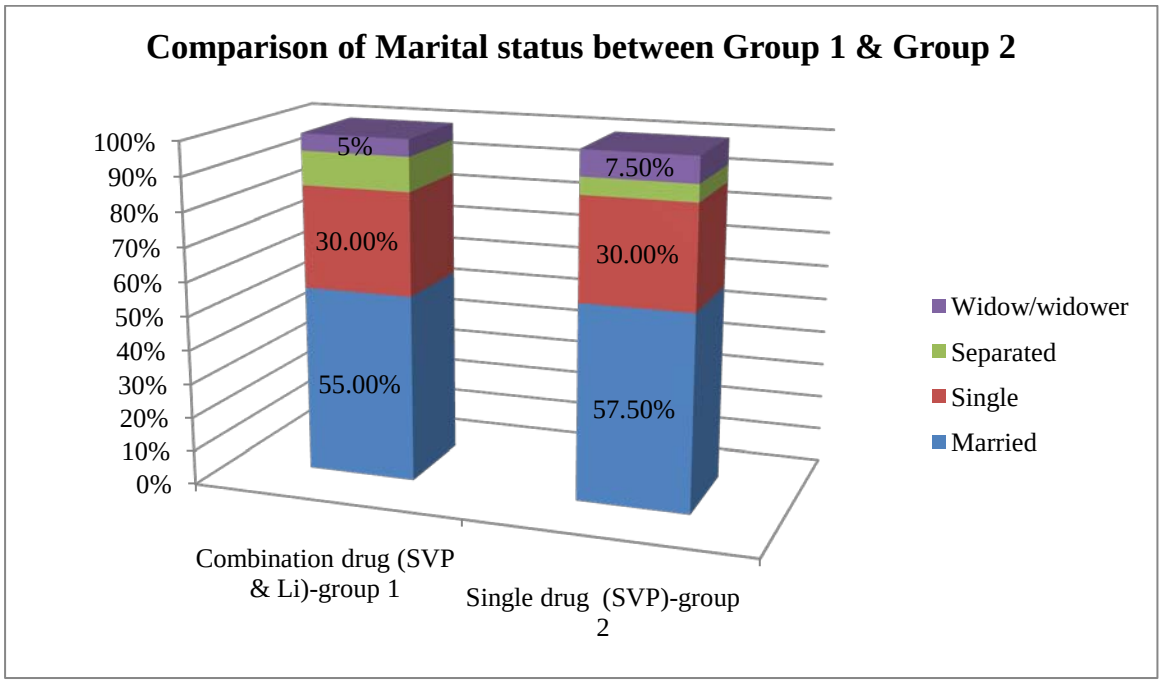
In group 1, 35% were unemployed (included housewives), 35% were in an unskilled profession while 30% were in a semi-skilled or skilled profession. In group 2, 42.5%, 27.5% and 30% were unemployed (housewives also), in an unskilled profession and in a semi-skilled or skilled profession respectively.

Chi-square test was applied for the sociodemogrphic comparison between the 2 groups. p values for all categories > 0.05, suggesting that there is no statistical significance between the two groups .

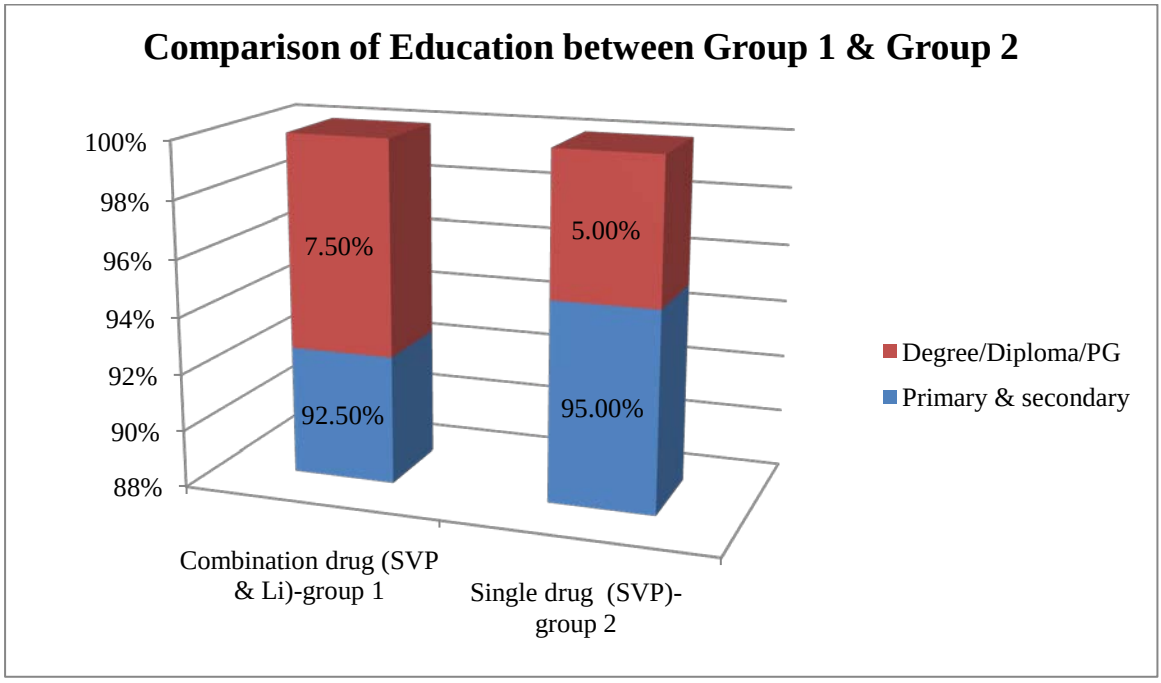
GRAPH 1a FOR TABLE-1



GRAPH 1b FOR TABLE 1



GRAPH 1c FOR TABLE 1



GRAPH 1d FOR TABLE 1

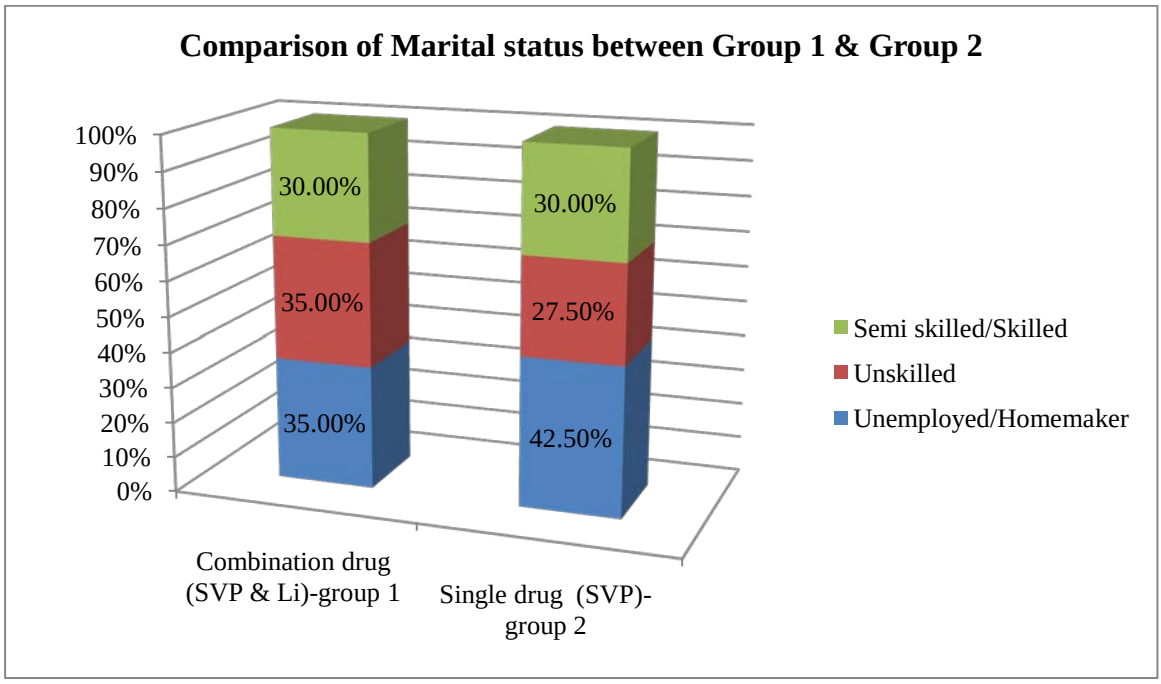


TABLE-2:

COMPARISON OF MEAN AGES OF THE TWO GROUPS

	Groups	N	Mean	Std. deviation	Std. error Mean	t value	p value
Age	Group 1 (SVP+Li)	40	36.675	9.804	1.550	0.124	0.902
	Group 2 (SVP)	40	36.400	10.030	1.586		

In this table, independent t-test was used to compare the mean ages of the 2 groups and as can be seen, the mean of the first group is 36.675 while that of the next is 36.4. As $p>0.05$, there is no statistical significance between the mean ages of the two groups.

GRAPH-2:

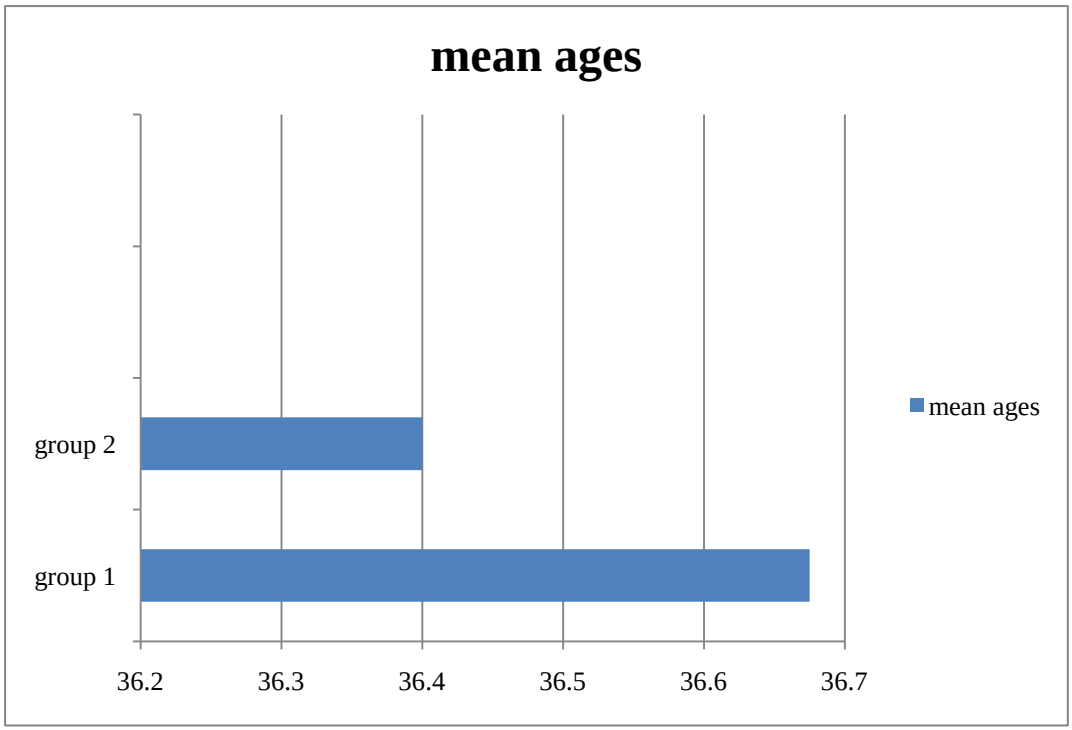


TABLE-3:

COMPARISON OF WHOQOL-BREF DOMAINS WITH SOCIODEMOGRAPHIC DATA

WHOQOL-BREF		Age	Sex	Education	Occupation
Physiological	Correlation coefficient	-.521**	.262*	.235*	.030
	P value	.000	.019	.036	.794
Psychological	Correlation Coefficient	-.590**	.256*	.137	.066
	P value	.000	.022	.226	.561
Social	Correlation Coefficient	-.496**	.285*	.205	.100
	P value	.000	.010	.068	.377
Environmental	Correlation Coefficient	-.564**	.261*	.171	.160
	P value	.000	.019	.130	.156

In this table, each domain of quality of life is compared with age using Pearson correlation test, and with gender, education and occupation with Spearmann Rank correlation test.

All 4 domains-physiological, psychological, social and environmental, were found to be negatively correlated with the age; that is the quality of life was found to be poorer with increasing age. Values are highly significant as $p<0.001$.

Every domain of the quality of life was found to be positively correlated with females.

Surprisingly, there was no effect of education on all the domains of quality of life other than the physiological domain. Also, the patients' occupation did not seem to affect the quality of life in any way.

TABLE-4

COMPARISON OF TOTAL WHOQOL-BREF SCORE WITH SOCIODEMOGRAPHIC DATA

		Age	**Sex**	**Education group**	**Occupation group**	**No. of episodes before treatment**
WHOQOL-BREF Total score	Correlation Coefficient	-.578**	.281*	.194	.114	-0.752**
	P value	p<.0001	.012	.084	.315	p<0.01
*. Correlation is significant at the 0.05 level (2-tailed)						
**. Correlation is significant at the 0.01 level (2-tailed)						

Total score WHOQOL-BREF= physiological + psychological + social + environmental

In this table, the quality of life as a whole was compared with the sociodemographic data as well as number of episodes before treatment, and as the previous table showed, quality of life was positively correlated with the female gender and negatively with age and pre-treatment number of episodes. Pearson correlation test was used to compare QOL with age and number of

episodes pre-treatment and Spearmann Rank correlation test for sex, education and occupation.

TABLE-5

COMPARISON OF GAF AND WHOQOL-BREF TOTAL SCORE BETWEEN THE TWO GROUPS:

	Group	N	Mean	Std. Deviation	Std. Error Mean	t value
GAF	Combination drug (SVP & Li)	40	8.075	1.3660	.2160	5.033*
	Single drug (SVP)	40	6.575	1.2987	.2053	
WHOQOL-BREF -total score	Combination drug (SVP & Li)	40	301.700	62.9930	9.9601	5.845*
	Single drug (SVP)	40	218.425	64.4248	10.1865	

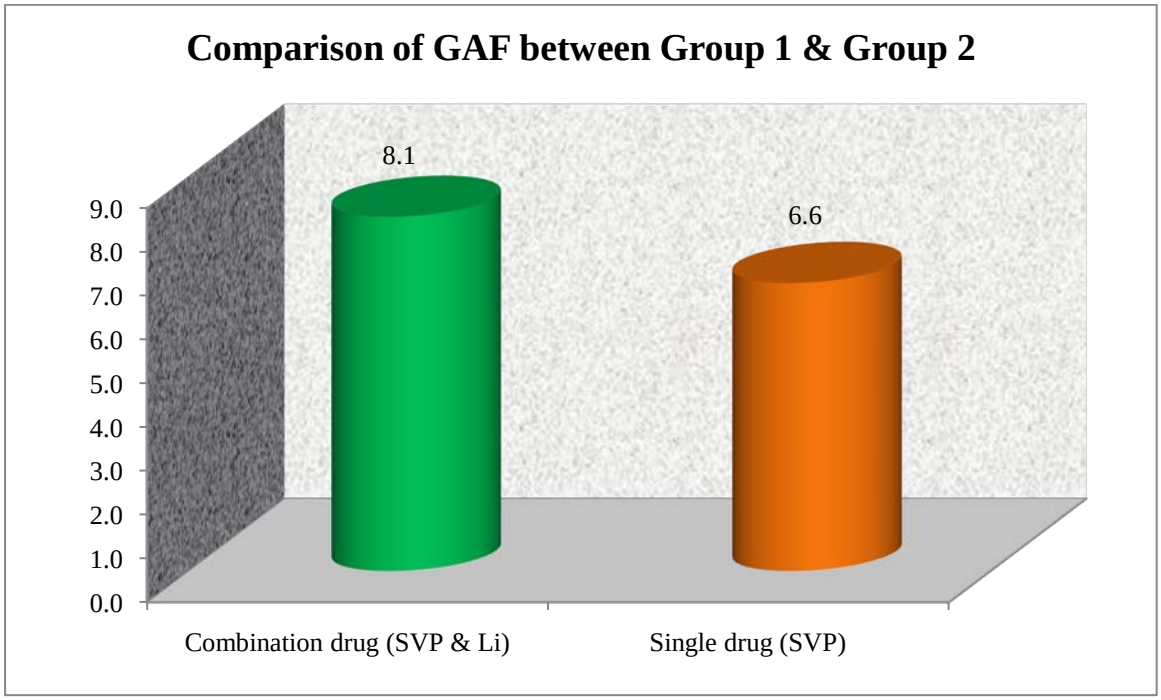
*p<0.001

Here, the functioning of patients as assessed by GAF (Global Assessment Functioning) and quality of life (QOL) assessed by the WHOQOL-BREF scale have been compared between the lithium and valproate combination therapy (group 1), and sodium valproate monotherapy (group 2) groups respectively. The GAF score which is usually given in a range, for eg: 91-100 was scored as 10, 81-90 as 9 and so on for statistical purposes.

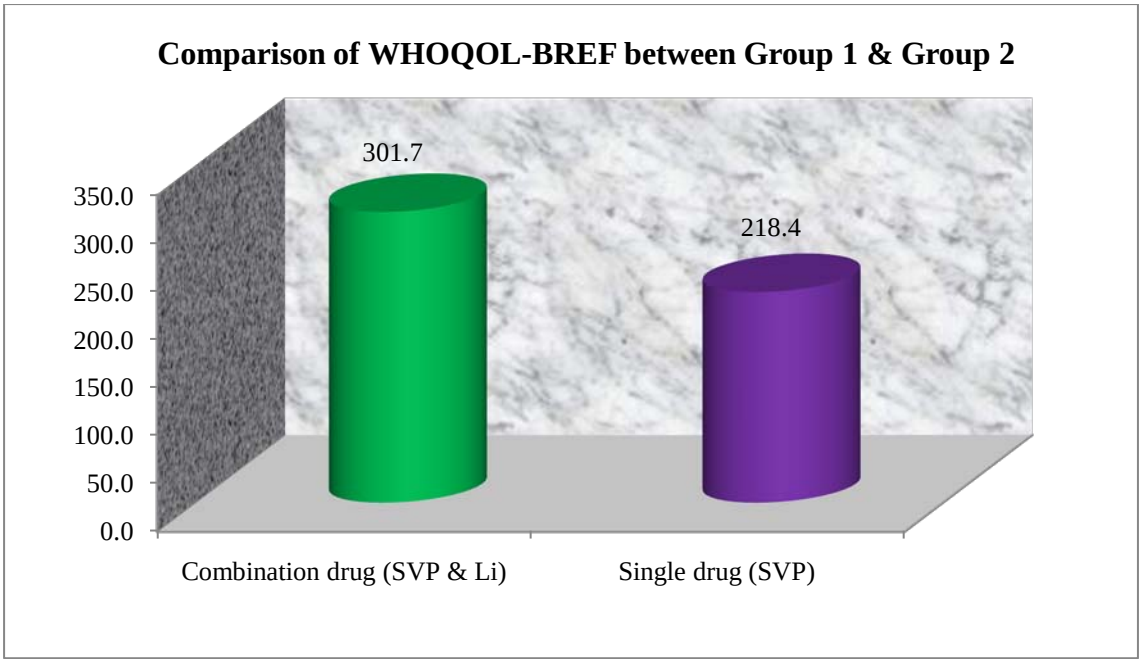
Independent-t test was applied, and it was found that both QOL and functioning were significantly better in the combination therapy group ($p<0.001$)

The mean GAF score in group 1 patients was found to be 8.075 with a standard deviation of 1.336 (8.075+/-1.336) while in group 2 they were 6.575 and 1.297 respectively (6.575+/-1.297) Clearly, GAF has been found to be better in the first group ($p<0.001$)

Also, the mean WHOQOL total score in group 1 patients was 301.7 and standard deviation was 62.992 (301.7+/-62.992) while in group 2, the mean was 218.425 and standard deviation was 64.425 respectively (218.425+/-64.425) Thus, the total WHOQOL score was more in group 1.



GRAPH 5a FOR TABLE 5



GRAPH 5b FOR TABLE -5

TABLE-6

COMPARISON OF WHOQOL-BREF DOMAINS

BETWEEN THE TWO GROUPS:

	Group	N	Mean	Std. Deviation	Std. Error Mean	t value
WHOQOL BREF-physiological	Combination drug (SVP & Li)	40	76.4000	14.31657	2.26365	7.160*
	Single drug (SVP)	40	50.8500	17.44816	2.75880	
WHOQOL BREF-psychological	Combination drug (SVP & Li)	40	73.6750	18.71704	2.95942	5.374*
	Single drug (SVP)	40	51.7750	17.72075	2.80190	
WHOQOL BREF-social	Combination drug (SVP & Li)	40	76.4750	16.57924	2.62141	4.827*
	Single drug (SVP)	40	57.4000	18.70253	2.95713	
WHOQOL BREF-environmental	Combination drug (SVP & Li)	40	75.1500	17.53027	2.77178	4.195*
	Single drug (SVP)	40	58.4000	18.17691	2.87402	

*p<0.001

In this table, QOL (each domain) of the patients have been compared between groups 1 and 2 using Independent-t test. The mean scores of QOL in each domain were as follows:

Physiological- 76.40+/-14.32 in group 1 and 50.85+/-17.45 in group 2

Psychological- 73.68+/-18.72 in group 1 and 51.78+/-17.72 in group 2

Social- 76.48+/-16.58 in group 1 and 57.40+/-18.70 in group 2

Environmental- 75.15+/-17.53 in group 1 and 58.40+/-18.18 in group 2

Thus, every domain of WHOQOL-BREF had a better score in group1 (combination therapy) as compared to group 2 (monotherapy) and the difference was significant ($p<0.001$)

GRAPH-6:

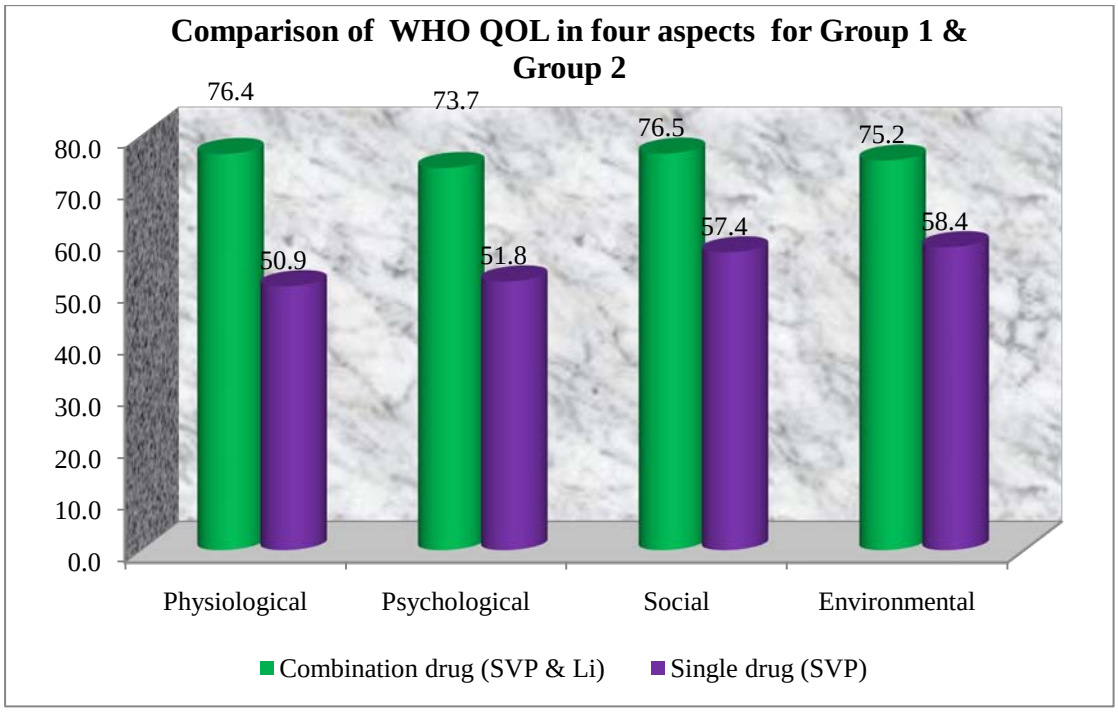


TABLE-7

COMPARISON OF COGNITIVE VARIABLES WITH

WHOQOL-BREF SCORE

Correlations		
		Total score WHOQOL-BREF
DF	Pearson Correlation	.610**
	P value	p <0.0001
DB	Pearson Correlation	.629**
	P value	p <0.0001
Stroop effect (secs)	Pearson Correlation	-.514**
	P value	p <0.0001
FAB total score	Pearson Correlation	.645**
	P value	p <0.0001
FAB-similarities	Pearson Correlation	.388**
	P value	p <0.0001
FAB-lexical fluency	Pearson Correlation	.489**
	P value	p <0.0001
FAB-Motor Luria	Pearson Correlation	.622**
	P value	p <0.0001
FAB-conflicting instructions	Pearson Correlation	.574**
	P value	p <0.0001
FAB:go-no-go	Pearson Correlation	.615**
	P value	p <0.0001
FAB-prehension behavior	Pearson Correlation	.526**
	P value	p <0.0001
TMT-A:time(secs)	Pearson Correlation	-0.461**
	P value	p <0.0001
TMT-B:time(secs)	Pearson Correlation	-0.610**
	P value	p <0.0001
**. Correlation is significant at the 0.01 level (2-tailed)		

In this table, Pearson correlation test has been applied to analyse whether there is any relationship between cognition and quality of life and results show that every domain of cognition tested with the following tests- Stroop test, TMT-A, TMT-B, digit forward and digit backward, are significantly correlated.

DF, DB, FAB total score as well as each component of FAB was found to be positively correlated with the quality of life, ie more the scores in these tests, better was the quality of life.

TMT-A, TMT-B and Stroop test were negatively correlated with quality of life, ie more the time taken to perform these tests, worse was the quality of life and vice-versa.

TABLE-8

COMPARISON OF FREQUENCY OF DEPRESSIVE EPISODES AFTER TREATMENT BETWEEN THE TWO GROUPS:

			Groups		Total
			Combination drug (SVP & Li)	Single drug (SVP)	
No of depressive episodes	0	Count	33	22	55
		% within group	82.5%	55.0%	68.8%
	1 & 2	Count	7	11	18
		% within group	17.5%	27.5%	22.5%
	3 and above	Count	0	7	7
		% within group	0.0%	17.5%	8.8%
Total		Count	40	40	80
		% within group	100.0%	100.0%	100.0%

Pearson Chi-Square=10.089* p=0.006

This table is to assess if there is any difference between the 2 groups in reducing the number of depressive episodes in the patients.

Using Pearson Chi-square test, (p=0.006), it was found that 7 people (17.5%) in group 2 had 3 or more depressive episodes following treatment, while no one in group 1 had 3 or more depressive episodes. 11 people (27.5%) in group 2 and 7 people (17.5%) in group 1 had 1 or 2 depressive episodes; while 33 people(82.5%) in group 1 and 22(55%) people in group 2 had no depressive episodes after administering the mood stabilizers.

Thus, the number of depressive episodes were found to be reduced in the group receiving both lithium and sodium valproate and around 82.5% of those receiving the combination had no depressive episodes after the therapy.

GRAPH-8:

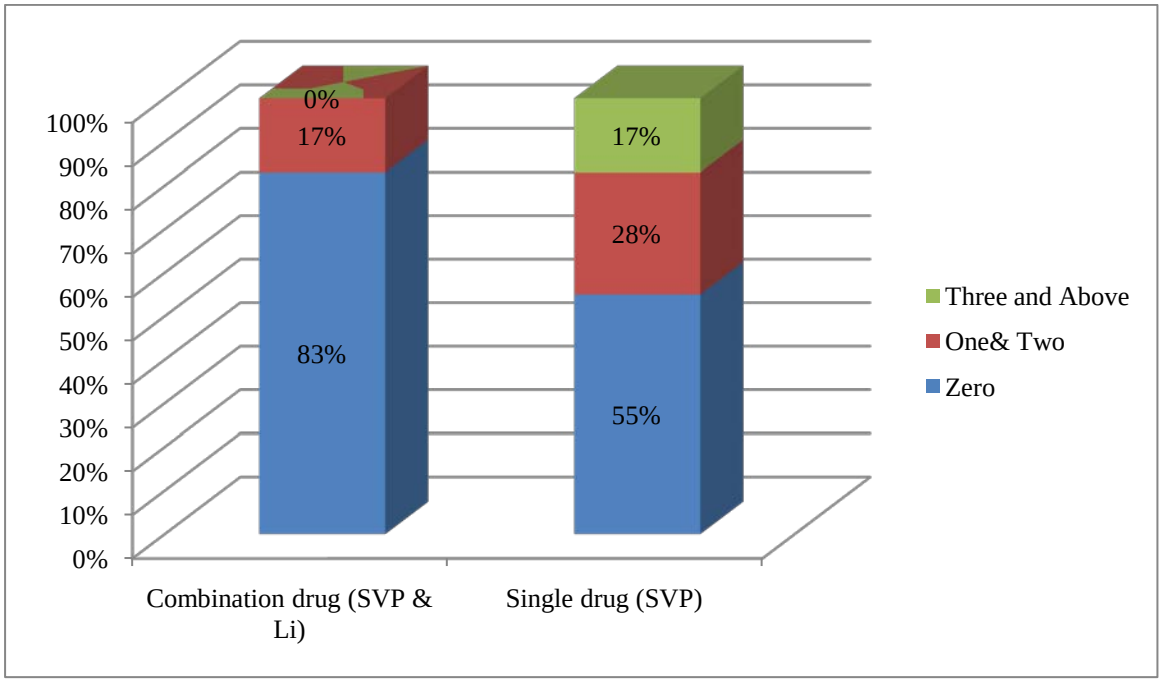


TABLE 9:

COMPARISON OF GROUP 1 NUMBER OF EPISODES

BEFORE & AFTER TREATMENT (SVP+Li):

	Mean	N	Std. Deviation	Std. Error Mean	t value
No.of episodes before treatment	4.900	40	3.8484	.6085	8.147**
No. of episodes after treatment (SVP+Li)	1.125	40	1.5053	.2380	

**p<0.001

In this table, paired t-test has been used to compare the means of the number of episodes in BPAD patients on the combination therapy, before and after treatment. A statistically significant difference has been noted, suggesting that SVP+Li has been effective in reducing the number of episodes.

TABLE 10:

COMPARISON OF GROUP 2 NUMBER OF EPISODES BEFORE &

AFTER TREATMENT (SVP):

	Mean	N	Std. Deviation	Std. Error Mean	t value
No. of episodes before treatment	5.0000	40	4.00641	0.63347	9.410**
No.of episodes after treatment (SVP)	4.0500	40	4.02524	0.63645	

**p<0.001

In this table, paired-t test has been used to compare the means of the number of episodes of BPAD patients on monotherapy, before and after treatment. Here also a statistically significant difference has been noted, suggesting that SVP alone also was found to be effective in reducing the episode frequency.

TABLE 11:

COMPARISON OF GROUPS 1 & 2 NUMBER OF EPISODES

BEFORE& AFTER TREATMENT:

	Groups	N	Mean	Std. Deviation	Std. Error Mean	t value
No.of episodes before treatment	Combination drug (SVP & Li)	40	4.900	3.8484	.60849	0.114 p=0.910
	Single drug (SVP)	40	5.000	4.0064	.63347	
No. of episodes after treatment	Combination drug (SVP & Li)	40	1.125	1.5053	.23801	4.305**
	Single drug (SVP)	40	4.050	4.0252	.63645	

**p<0.001

In this table, independent t test has been used to compare the number of episodes before treatment in groups 1 and 2, and after treatment, in both the groups. The difference was statistically significant after treatment, wherein the combination therapy was found to reduce the episode frequency more, while before treatment, no difference was noted.

GRAPH 12:

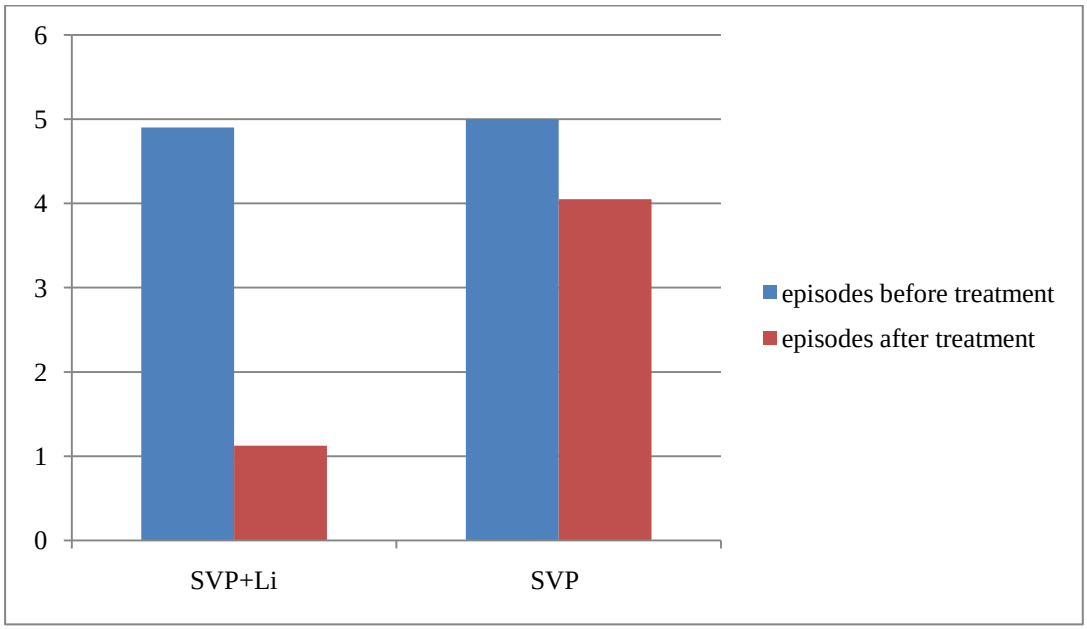

6
5
4
3
2
1
0
SVP+Li
SVP
episodes before treatment
episodes after treatment

TABLE-13

COMPARISON OF COGNITIVE VARIABLES

BETWEEN THE TWO GROUPS:

Group		N	Mean	Std. Deviation	Std. Error Mean	t value	p value
DF	Combination drug (SVP & Li)	40	4.4500	1.41331	.22346	0.085	0.932
	Single drug (SVP)	40	4.4750	1.19802	.18942		
DB	Combination drug (SVP & Li)	36	3.9167	1.38099	.23017	0.91	0.366
	Single drug (SVP)	38	3.6053	1.55162	.25171		
Stroop test :time(secs)	Combination drug (SVP & Li)	40	279.28	49.120	7.767	0.585	0.560
	Single drug (SVP)	40	272.28	57.566	9.102		
FAB total score	Combination drug (SVP & Li)	40	14.6250	3.27921	.51849	0.129	0.898
	Single drug (SVP)	40	14.5250	3.63732	.57511		
FAB-similarities	Combination drug (SVP & Li)	40	2.5500	.59700	.09439	1.359	0.178
	Single drug (SVP)	40	2.7250	.55412	.08761		
FAB-lexical fluency	Combination drug (SVP & Li)	40	2.3000	.68687	.10860	0.641	0.524
	Single drug (SVP)	40	2.4000	.70892	.11209		
FAB-Motor Luria	Combination drug (SVP & Li)	40	1.9750	.89120	.14091	0.127	0.9
	Single drug (SVP)	40	1.9500	.87560	.13844		

FAB-conflicting instructions	Combination drug (SVP & Li)	40	2.5500	.71432	.11294	1.027	0.307
	Single drug (SVP)	40	2.3750	.80662	.12754		
FAB-go-no-go test	Combination drug (SVP & Li)	40	2.6000	.59052	.09337	1.371	0.174
	Single drug (SVP)	40	2.4000	.70892	.11209		
FAB-prehension behavior	Combination drug (SVP & Li)	40	2.7000	.46410	.07338	0.225	0.822
	Single drug (SVP)	40	2.6750	.52563	.08311		
TMT-A:time(secs)	Combination drug (SVP & Li)	40	55.83	23.431	3.705	1.756	0.083
	Single drug (SVP)	40	47.35	19.561	3.093		
TMT-B:time(secs)	Combination drug (SVP & Li)	40	273.18	26.746	4.229	-0.293	0.771
	Single drug (SVP)	40	275.03	29.714	4.698		

In this table, Independent-t test has been used to compare the cognition variables among the 2 groups.

None of the results were significant as $p > 0.05$ for all the variables.

However, combination therapy fared better than the monotherapy in the following tests-digit backward, stroop test (lesser time), FAB total score, FAB-motor luria and conflicting instructions though the results are insignificant.

TABLE-14

COMPARISON OF COGNITIVE VARIABLES WITH SOCIODEMOGRAPHIC DATA AND TOTAL NUMBER OF EPISODES DURING ILLNESS:

		Age	Sex	Education group	No.of episodes
DF	Correlation Coefficient	-.655**	.316**	.291**	-.656**
	P Value	.000	.004	.009	.000
DB	Correlation Coefficient	-.588**	.202	.323**	-.666**
	P Value	.000	.084	.005	.000
Stroop test: time(secs)	Correlation Coefficient	.603**	-.227	-.013	.740**
	P Value	.000	.083	.489	.000
FAB total score	Correlation Coefficient	-.721**	.250*	.272*	-.743**
	P Value	.000	.025	.015	.000
FAB-similarities	Correlation Coefficient	-.555**	.195	.068	-.584**
	P Value	.000	.083	.551	.000
FAB-lexical fluency	Correlation Coefficient	-.658**	.292**	.172	-.637**
	P Value	.000	.009	.127	.000
FAB-Motor Luria	Correlation Coefficient	-.600**	.194	.325**	-.609**
	P Value	.000	.085	.003	.000
FAB-conflicting instructions	Correlation Coefficient	-.588**	.206	.200	-.601**
	P Value	.000	.067	.076	.000
FAB:go-no-go	Correlation Coefficient	-.567**	.128	.211	-.600**
	P Value	.000	.258	.060	.000
FAB-prehension behavior	Correlation Coefficient	-.580**	.228*	.169	-.557**
	P Value	.000	.042	.135	.000
TMT-A:time(secs)	Correlation Coefficient	.559**	-.203*	-.144	.797**
	P Value	.000	.036	.615	.000
TMT-B:time(secs)	Correlation Coefficient	.631**	-.201*	-.135	.886**
	P Value	.000	.040	.783	.000

*. Correlation is significant at the 0.05 level (2-tailed)

**. Correlation is significant at the 0.01 level (2-tailed)

By Pearson correlation statistics age has been found to be correlated negatively with some cognitive variables-DF, DB, each component of FAB and total score, ie, younger people were able to repeat more digits forward and backward. Younger people were able to perform FAB better, ie, they had better FAB scores, so was the case with the individual component-ie people with lesser age were able to tell more similarities, more words in FAS test, did lesser mistakes in go-no-go test, conflicting instructions test, prehension behavior and motor-luria test; ie they scored better in these tests, while older people scored comparatively lesser. Age was positively correlated with other variables-TMT-A, TMT-B; ie lesser the age, lesser was the time taken to complete the test and lesser were the errors performed.

Males were found to perform DF and DB, FAB-all components better than females, and worse in Stroop test, TMT-A and TMT-B.

Also education was found to be positively correlated with DF, DB(with high significance-$p<0.01$), FAB-total($p<0.05$) and individual component motor-luria test with high significance while other components correlation were insignificant($p>0.05$) Thus, patients with better education were able to repeat more number of digits backwards and forwards, had a better FAB total score and scored high on motor luria test.

Though insignificant, education was negatively correlated with the time taken to perform Stroop test and TMT-A test and the errors in Stroop test,

TMT-A and TMT-B; ie, lower the education, more was the time taken to perform the above said tests and more were the errors noticed.

The total number of episodes of illness were found to be correlated with the cognitive variables with high significance($p<0.01$)- negatively correlated with DF, DB, FAB-total and individual scores; and positively correlated with the remaining. Therefore, those with fewer number of episodes were able to repeat more digits forward and backward, scored better in the total as well as individual components of FAB, took lesser time to complete Stroop test, TMT-A, TMT-B and made fewer errors in Stroop test, TMT-A and TMT-B tests.

DISCUSSION

In our study, the functioning assessed by GAF, was found to be better in the group of patients who were treated with the combination of SVP and lithium. This finding is not supported by BALANCE study as though the GAF was better in the combination therapy group, it was not found to be statistically significant [17].

The quality of life in our study was found to be better in the group receiving sodium valproate and lithium when compared to the group receiving only sodium valproate. This is also in contradiction to BALANCE as though the quality of life was slightly better in the combination group, the difference was insignificant in the BALANCE study [17].

Many studies have reported that the combination of lithium and sodium valproate is better than sodium valproate, in terms of faster reductions of mania rating scores [2, 108]. Few studies report that use of lithium improves quality of life by lowering medical costs [153] and use of lithium in euthymic bipolar patients showed better quality of life, comparable to healthy controls, when compared to patients with schizophrenia [113].

Geddes and colleagues found clear superiority of lithium compared to valproate, with the combination marginally better than lithium alone [8], also supporting our study.

In our study, the combination therapy was found to reduce the number of episodes after treatment more than the monotherapy alone. This finding is

supported by a study done by Xu et al, who also found that in bipolar patients, rates of relapse were markedly lower in patients on the combination therapy when compared to the monotherapies [107]. A study by Liu et al also found that the combination of lithium and sodium valproate was more effective than the lithium monotherapy in relapse prevention [19]. This is supported by a study done by Neeli et al [2] who reported that the number of episodes following treatment was found to be significantly reduced in the group receiving the combination therapy when compared to the group receiving monotherapy..

Similar findings have been reported in few other studies, but when compared with lithium monotherapy and in rapid cycling type, substantiating the superior efficacy of lithium and sodium valproate combination [96,106].

In our study, though results were not statistically significant, FAB-lexical fluency was found to be worse in the combination therapy which is supported by the study done by Vasile et al who reported that lithium was found to be associated with decreased verbal fluency but this could be accounted for by the use of valproate which is associated with slowing of reaction time, memory and minor learning deficits [117].

The same study reported lower motor performance memory [117], which contradicts our study results, in which FAB-motor luria, conflicting instructions and digit backward were performed better by the combination group, though the differences are not statistically significant.

The total number of episodes of illness in our study was found to be associated with performance in the cognitive tests. Those with fewer number of episodes were able to repeat more digits forward and backward, scored better in the total as well as individual components of FAB, took lesser time to complete Stroop test, TMT-A, TMT-B. This is supported by many studies wherein it was reported that cognition was affected negatively with increase in the number of episodes [20, 36].

In our study, WHOQOL total score was inversely associated with the number of episodes; ie lesser the number of episodes of illness before treatment, more was the score. This is supported by another study which reported that patients with more episodes had a poorer quality of life [43].

In our study, the cognitive impairment was found to be associated with a lower quality of life and vice-versa. This is supported by many studies, [16,20] which report that impairment in cognitive functioning, especially memory disturbances, can in turn affect functional outcome of patients with bipolar disorder, negatively.

In our study there was no difference in the cognitive functioning between the 2 groups, but the quality of life was found to be better in the group receiving combination therapy. Studies that tested cognition on euthymic bipolar patients mostly with individual treatment, either on lithium or sodium valproate have been done.

In some individual studies done with patients on lithium, neuroimaging also supports that lithium exerts neuroprotective action. This has been extensively also reported in animal studies. For example, lithium when used for four weeks as treatment in bipolar patients, was shown to increase grey-matter content of the brain, in a study that involved 3-D magnetic resonance imaging [33] as well as hippocampal volume, in another [34], thereby concluding that this effect probably occurred as a result of neurotrophic effects.

A meta-analysis involving 12 studies with 276 subjects taking lithium for around 3.9 years, concluded that only few minor negative effects on cognition were observed [28]. All these studies conclude the possibility that lithium may not provide cognitive enhancement, but may protect from cognitive deterioration over the long-term. Thus, literature regarding effects of lithium on cognition is mixed.

Sodium valproate has been associated with mild memory and attentional dose-dependent impairments, reductions in verbal memory and increased decision time, without accompanying visual and spatial processing alterations [20,22,32].

The comparison of bipolar euthymic outpatients treated with lithium, with those on valproate and control subjects showed that immediate memory was affected similarly in both groups actively treated, which suggest an intrinsic deficit of bipolar disorder or a common substrate of lithium and valproate influences on immediate verbal memory [20].

In our study, the number of depressive episodes reported after being on treatment with mood stabilisers was found to be much lesser in the combination group when compared to the group on valproate monotherapy. Likewise, lithium has been found to have a decreased rate of suicide compared with valproate in many studies [154].

CONCLUSIONS

1. The quality of life of those euthymic bipolar patients on the combination therapy of lithium and sodium valproate was found to be better than those on the valproate monotherapy.

2. Every domain- physical, physiological, social and environmental domains were found to be better in those receiving the combination therapy than the monotherapy.

3. The functioning of those euthymic bipolar patients on the lithium and sodium valproate combination therapy was found to be better than those on the valproate monotherapy alone.

4. There was no difference in the cognitive domains tested-memory, attention and executive functions between the two groups.

5. The number of manic and depressive episodes following treatment were found to be much lesser in those receiving the combination therapy.

6. Cognition was found to affect the quality of life inversely.

STRENGTHS

1. Age, gender and education were matched between the two groups.

2. Comparing cognition between these two groups has not been done extensively in the past.

LIMITATIONS

1. As patients were recruited from single centre only (Institute of Mental Health) and being a hospital based study, the results cannot be generalized to the entire population.
2. The use of other drugs- antipsychotics, benzodiazepines, anticholinergics etc was not controlled or stopped, which could have affected the cognition negatively.
3. A longitudinal study could have been a better design.
4. The use of controls could have raised the power of the study.
5. Since some of the episodes of the illness were told from the patient's memory, as opposed to getting details from the records, some amount of recall bias could have affected the results.
6. As the Sample size is lower, some of the statistical power might not be significant in the results for major inferences to be drawn.
7. Due to the lack of funds, the serum levels of lithium were not done; though no side effects were noted in the patients.

FUTURE DIRECTIONS

1. Multi-centre study would help in gathering a large sample for study obtaining a heterogeneous sample and hence generalization of study results.

2. Follow-up study would help in studying prognosis of the study.

3. Methods to reduce bias to be handled in all steps of study.

4. Controls may be included.

5. Lithium clinic may be helpful in looking for the serum lithium levels and monitor on a regular basis.

6. Neuroimaging studies can be done to assess the cognitive impairment.

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SOCIODEMOGRAPHIC PROFORMA

COMPARISON OF LITHIUM AND SODIUM VALPROATE COMBINATION THERAPY WITH SODIUM VALPROATE MONOTHERAPY IN EUTHYMIC BIPOLAR PATIENTS

S.No: OP No: Unit: Date:

Name: Age: Sex:

Occupation: Education:

Income:

Marital status: Language:

Address: Phone number:

Name of the informant: Relationship:

No. of years living with the patient:

Duration of illness:

Age of onset:

Total number of manic/depressive episodes:

Current treatment:

Comorbid substance use:

Duration of treatment:

No. of episodes after treatment-depressive/manic:

Other illness:

Current medications:

1. YMRS :
2. HAMD :
3. GAF :
4. WHOQOL-BREF :physiological :

   Psychological :

   Social :

   Environmental :
5. FAB :

   Similarities task

   Phonological fluency task

   Luria’s motor series

   Conflicting instructions task

   Go-no-go task

   Prehension behavior
6. TMT-A :
7. TMT-B :
8. Digit forward :
9. Digit backward :
10. Stroop test :

ஆராய்ச்சி தகவல் தாள்

ஆராய்ச்சி தலைப்பு : கூனமடந்த உணர்ச்சி கோளாறு நோயாளிகளுக்கு சோடியம் வால்ப்ரோயேட் ஒற்றை சிகிச்சை மோனோ லித்தியம் மற்றும் சோடியம் வால்ப்ரோயேட் கூட்டு சிகிச்சை ஒப்பீடு

ஆய்வாளர் : அஷ்வின் மூத்தசாமி

பங்கேற்பவர் பெயர் :

இடம் : அரசு மனநல காப்பகம்
சென்னை- 600010

தாங்கள் இந்த ஆராய்ச்சியில் பங்குபெறுவதற்கேற்ப தகவல்கள் கொடுக்கப்பட்டுள்ளது. தங்கள் சந்தேகங்களை கேட்டு அறிந்து கொள்ளலாம்.

ஆராய்ச்சியின் நோக்கம் :
இருமுனை உணர்ச்சி கோளாறு அலைக்கழிக்கிறது மேலும் அதில் அறிவாற்றல் சரிவு ஏற்படும். இந்த ஆய்வில் வெவ்வேறு மருந்துகள் கிடைக்கும் இரண்டு குழுகளின் இடையே ஒப்பீடு செய்வதே நோக்கம்.

ஆராய்ச்சி முறை :
புறநோயாளியாக வரும்பொழுது உங்கள் விருப்பத்துடன் பரிசோதனை செய்யப்படும்.

இந்த ஆய்வின் முடிவுகளை ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிக்கப்படும் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்க்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எநநேரமும் இந்த ஆராய்ச்சியில் இருந்து பின் வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

மேலுவகளை அல்லது கருத்தகளை வெளியிடும் பநேரோ அல்லது ஆராய்ச்சியின் பநேரோ தங்களது பயெரயைோ அல்லது அடையாளங்களையோ வெளியிடமாட்டடோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையெப்பம்: பங்கேற்பாளர் கையெப்பம்:
இடம்:
தேதி:

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு: சுனமடைந்த இருமுனை உணர்ச்சி கோளாறு நோயாளிகளுக்கு சோடியம் வால்ப்ரோயேட் ஒற்றை சிகிச்சையுடனான லித்தியம் மற்றும் சோடியம் வால்ப்ரோயேட் கூட்டு சிகிச்சை ஒப்பீடு

பங்கு கொள்பவர் பெயர்:

ஆய்வாளர்: அஷ்வின் மூத்தசாமி
மருத்துவ நிலையம்: அரசு மனநல காப்பகம்
சென்னை- 600010

..... எனும் நான் எனக்கு கொடுக்கப்பட்ட தகவல் தாளினை படித்து புரிந்துக கொண்டேன். என்னுடைய சுய நினைவுடனும் மற்றும் முழு சுதந்திரத்துடனும் இந்த ஆராய்ச்சியில் என்னை சேர்த்துக்க கொள்ள சம்மதிக்கிறேன்.

எனக்கு இந்த ஆராய்ச்சியின் ஒப்புதல் படிவம் விளக்கப்பட்டது.

எனக்கு இந்த ஆராய்ச்சியின் நோக்கமும், விவரங்களும் விளக்கப்பட்டது.

எனக்கு என்னுடைய உரிமைகளை பற்றி விளக்கப்பட்டது.

நான் இதுவரை எடுத்துக்க கொண்ட அனைத்து மருத்துவ முறைகளைப் பற்றி தெரிவித்திருக்கிறேன்.

இந்த ஆராய்ச்சியில் இருந்து எந்நேரமும் பின் வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்துக கொண்டேன்.

என்னை பற்றிய எந்த தகவல்களும், அடையாளமும் வெளியிடப்பட மாட்டாது என்பதை புரிந்துக நொண்டேன்.

என்னை பற்றிய எந்த தகவல்களும், அடையாளமும் வெளியிடப்பட மாட்டாது என்பதை நான் புரிந்துக கொண்டேன்.

என்னுடைய முழு சுதந்திரத்தோடும் இந்த ஆராய்ச்சியில் என்னை சேர்த்துக்க கொள்ள சம்மதிக்கிறேன்.

பங்கேற்பாளர் பெயர் மற்றும் கையெப்பம்.....தேதி:.....

பாதுகாவலர் பெயர் மற்றும் கையெப்பம்.....தேதி:.....

INFORMATION TO PARTICIPANTS

Title : COMPARISON OF LITHIUM AND SODIUM VALPROATE COMBINATION THERAPY WITH SODIUM VALPROATE MONOTHERAPY IN EUTHYMIC BIPOLAR PATIENTS

Principal Investigator : Dr. Ashwini Muthusamy
II Year, MD Psychiatry Post Graduate
Madras Medical College, Chennai.
Co-Investigator (if any) :
Name of Participant :
Site : IMH, MMC, Chennai
You are invited to take part in this research. The information in this document is meant to help you decide
whether or not to take part. Please feel free to ask if you have any queries or concerns.

What is the purpose of research?
Bipolar affective disorder can be accompanied by some impairment of functioning in day to day life, mainly in neurocognitive functioning . We want to compare and find out how certain medications/combinations used for maintenance can affect the neurocognition of patients. We have obtained permission from the Institutional Ethics Committee.

The study design
You will be interviewed on OP basis while you visit our hospital for review.

Study procedures
The study involves evaluation of quality of life as well as effect on neurocognition with the current medications.
You will be required to spare roughly half an hour for a one-time interview during your visit to the hospital.

Possible benefits to other people
The results of the research may provide benefits to the society in terms of advancement of medical knowledge and / or therapeutic benefit to future patients.

Confidentially of the information obtained from you
You have the right to confidentially regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigations, other study personnel and the Institutional Ethics Committee, to view your data, if required.The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?
Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. You will be taken care of and you will not lose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?
The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, it is advisable that you talk to the research team prior to stopping the treatment / discontinuing of procedures etc.

Signature of Investigator
Signature of Participant
Date:

INFORMED CONSENT FORM

Title : **COMPARISON OF LITHIUM AND SODIUM VALPROATE COMBINATION THERAPY WITH SODIUM VALPROATE MONOTHERAPY IN EUTHYMIC BIPOLAR PATIENTS**

Name of the Participant :
Name of Principal/Co-Investigator : Dr. Ashwini Muthusamy
Name of Institution : IMH, MMC, Chennai.
Name and address of the sponsor / agency(ies), if any: _____
I _____(name of participant), have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am exercising my free power of choice,hereby give my consent to be included as a participant in "COMPARISON OF LITHIUM AND SODIUM VALPROATE COMBINATION THERAPY WITH SODIUM VALPROATE MONOTHERAPY IN EUTHYMIC BIPOLAR PATIENTS".

1) I have read and understood this consent form and the information provided to me.
2) I have had the consent document explained to me.
3) I have been explained about the nature of the study.
4) I have been explained about my rights and responsibilities by the investigator.
5) I have informed the investigator of all the treatments I am taking or have taken in the past, including any native (alternative) treatments.
6) I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in the hospital.
7) I hereby give permission to the investigators to release the information obtained from me as a result of participation in this study to the regulatory authorities, Government agencies, and ethics committee. I understand that they may inspect my original records.
8) I understand that my identity will be kept confidential if my data are publicly presented.
9) I have had my questions answered to my satisfaction.
10) I consent voluntarily to participate as a participant in the research study. I am aware, that I can opt out of the study, I should contact the investigators. By signing this consent from, I attest that the information given in this document has been clearly explained to me and understood by me. I will be given a copy of this consent document.

For adult participants

Name and signature / thumb impression of the participant (or legal representative if participant is incompetent):

(Name)_____ (Signature) _____Date:_____

Name and signature of impartial witness (required for illiterate patients):

(Name)_____ (Signature) _____Date:_____

Address and contact number of the impartial witness:_____

Name and signature of the investigator or his representative obtaining consent:

(Name)_____ (Signature) _____Date: _____

WHO/MSA/MNH/PSF/97.4
English only
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WHOQOL-BREF

PROGRAMME ON MENTAL HEALTH
WORLD HEALTH ORGANIZATION
GENEVA

For office use only

	Equations for computing domain scores	Raw score	Transformed scores*	
Domain 1	(6-Q3) + (6-Q4) + Q10 + Q15 + Q16 + Q17 + Q18 ☐ + ☐ + ☐ + ☐ + ☐ + ☐ + ☐	=	**4-20**	**0-100**
Domain 2	Q5 + Q6 + Q7 + Q11 + Q19 + (6-Q26) ☐ + ☐ + ☐ + ☐ + ☐ + ☐	=		
Domain 3	Q20 + Q21 + Q22 ☐ + ☐ + ☐	=		
Domain 4	Q8 + Q9 + Q12 + Q13 + Q14 + Q23 + Q24 + Q25 ☐ + ☐ + ☐ + ☐ + ☐ + ☐ + ☐ + ☐	=		

* Please see Table 4 on page 10 of the manual, for converting raw scores to transformed scores.

I.D. number

ABOUT YOU

Before you begin we would like to ask you to answer a few general questions about yourself: by circling the correct answer or by filling in the space provided.

What is your **gender**? Male Female

What is you **date of birth**? _____ / _____ / _____
Day / Month / Year

What is the highest **education** you received?
None at all
Primary school
Secondary school
Tertiary

What is your **marital status**?
Single Separated
Married Divorced
Living as married Widowed

Are you currently **ill**? Yes No

If something is wrong with your health what do you think it is?_____illness/ problem

Instructions

This assessment asks how you feel about your quality of life, health, or other areas of your life. **Please answer all the questions.** If you are unsure about which response to give to a question, **please choose the one** that appears most appropriate. This can often be your first response.

Please keep in mind your standards, hopes, pleasures and concerns. We ask that you think about your life **in the last two weeks.** For example, thinking about the last two weeks, a question might ask:

		Not at all	Not much	Moderately	A great deal	Completely
	Do you get the kind of support from others that you need?	1	2	3	4	5

You should circle the number that best fits how much support you got from others over the last two weeks. So you would circle the number 4 if you got a great deal of support from others as follows.

		Not at all	Not much	Moderately	A great deal	Completely
	Do you get the kind of support from others that you need?	1	2	3	4	5

You would circle number 1 if you did not get any of the support that you needed from others in the last two weeks.

Please read each question, assess your feelings, and circle the number on the scale for each question that gives the best answer for you.

		Very poor	Poor	Neither poor nor good	Good	Very good
1(G1)	How would you rate your quality of life?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
2 (G4)	How satisfied are you with your health?	1	2	3	4	5

The following questions ask about **how much** you have experienced certain things in the last two weeks.

		Not at all	A little	A moderate amount	Very much	An extreme amount
3 (F1.4)	To what extent do you feel that physical pain prevents you from doing what you need to do?	1	2	3	4	5
4(F11.3)	How much do you need any medical treatment to function in your daily life?	1	2	3	4	5
5(F4.1)	How much do you enjoy life?	1	2	3	4	5
6(F24.2)	To what extent do you feel your life to be meaningful?	1	2	3	4	5

		Not at all	A little	A moderate amount	Very much	Extremely
7(F5.3)	How well are you able to concentrate?	1	2	3	4	5
8 (F16.1)	How safe do you feel in your daily life?	1	2	3	4	5
9 (F22.1)	How healthy is your physical environment?	1	2	3	4	5

The following questions ask about **how completely** you experience or were able to do certain things in the last two weeks.

		Not at all	A little	Moderately	Mostly	Completely
10 (F2.1)	Do you have enough energy for everyday life?	1	2	3	4	5
11 (F7.1)	Are you able to accept your bodily appearance?	1	2	3	4	5
12 (F18.1)	Have you enough money to meet your needs?	1	2	3	4	5
13 (F20.1)	How available to you is the information that you need in your day-to-day life?	1	2	3	4	5
14 (F21.1)	To what extent do you have the opportunity for leisure activities?	1	2	3	4	5

		Very poor	Poor	Neither	Good	Very good

				poor nor good		
15 (F9.1)	How well are you able to get around?	1	2	3	4	5

The following questions ask you to say how **good or satisfied** you have felt about various aspects of your life over the last two weeks.

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
16 (F3.3)	How satisfied are you with your sleep?	1	2	3	4	5
17 (F10.3)	How satisfied are you with your ability to perform your daily living activities?	1	2	3	4	5
18(F12.4)	How satisfied are you with your capacity for work?	1	2	3	4	5
19 (F6.3)	How satisfied are you with yourself?	1	2	3	4	5
20(F13.3)	How satisfied are you with your personal relationships?	1	2	3	4	5
21(F15.3)	How satisfied are you with your sex life?	1	2	3	4	5
22(F14.4)	How satisfied are you with the support you get from your friends?	1	2	3	4	5
23(F17.3)	How satisfied are you with the conditions of your living place?	1	2	3	4	5
24(F19.3)	How satisfied are you with your access to health services?	1	2	3	4	5
25(F23.3)	How satisfied are you with your transport?	1	2	3	4	5

The following question refers to **how often** you have felt or experienced certain things in the last two weeks.

		Never	Seldom	Quite often	Very often	Always
26 (F8.1)	How often do you have negative feelings such as blue mood, despair, anxiety, depression?	1	2	3	4	5

Did someone help you to fill out this form?.....

How long did it take to fill this form out?.....

Do you have any comments about the assessment?

.....

.....

THANK YOU FOR YOUR HELP

Global Assessment of Functioning (GAF) Scale

(From DSM-IV-TR, p. 34.)

Consider psychological, social, and occupational functioning on a hypothetical continuum of mental health-illness. Do not include impairment in functioning due to physical (or environmental) limitations.

Code	(Note: Use intermediate codes when appropriate, e.g., 45, 68, 72.)
100 | 91	**Superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his or her many positive qualities. No symptoms.**
90 | 81	**Absent or minimal symptoms** (e.g., mild anxiety before an exam**), good functioning in all areas, interested and involved in a wide range of activities. socially effective, generally satisfied with life, no more than everyday problems or concerns** (e.g. an occasional argument with family members).
80 | 71	**If symptoms are present, they are transient and expectable reactions to psychosocial stressors** (e.g., difficulty concentrating after family argument); **no more than slight impairment in social, occupational or school functioning** (e.g., temporarily failing behind in schoolwork).
70 | 61	**Some mild symptoms** (e.g. depressed mood and mild insomnia) **OR some difficulty in social, occupational, or school functioning** (e.g., occasional truancy, or theft within the household)**, but generally functioning pretty well, has some meaningful interpersonal relationships.**
60 | 51	**Moderate symptoms** (e.g., flat affect and circumstantial speech, occasional panic attacks) **OR moderate difficulty in social, occupational, or school functioning** (e.g.. few friends, conflicts with peers or co-workers).
50 | 41	**Serious symptoms** (e.g.. suicidal ideation, severe obsessional rituals, frequent shoplifting) **OR any serious impairment in social, occupational, or school functioning** (e.g., no friends, unable to keep a job).
40 | 31	**Some impairment in reality testing or communication** (e.g., speech is at times illogical, obscure, or irrelevant) **OR major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood** (e.g., depressed man avoids friends, neglects family, and is unable to work; child frequently beats up younger children, is defiant at home, and is failing at school).
30 | 21	**Behavior is considerably influenced by delusions or hallucinations** **OR serious impairment in communication or judgment** (e.g., sometimes incoherent, acts grossly inappropriately, suicidal preoccupation) **OR inability to function in almost all areas** (e.g., stays in bed all day; no job, home, or friends).
20 | 11	**Some danger of hurting self or others** (e.g., suicide attempts without clear expectation of death; frequently violent; manic excitement) **OR occasionally fails to maintain minimal personal hygiene** (e.g., smears feces) **OR gross impairment in communication** (e.g., largely incoherent or mute).
10 | 1	**Persistent danger of severely hurting self or others** (e.g., recurrent violence) **OR persistent inability to maintain minimal personal hygiene** **OR serious suicidal act with clear expectation of death.**
0	Inadequate information.

ANNEXURE

FRONTAL ASSESSMENT BATTERY

1. Similarities (conceptualization)

"In what way are they alike?"

- A banana and an orange
- A table and a chair
- A tulip, a rose and a daisy

Score (only category responses [fruits, furniture, flowers] are considered correct)

Three correct: 3 Two correct: 2 One correct: 1 None correct: 0

2. Lexical fluency (mental flexibility)

"Say as many words as you can begin with the letter 'S,' any words except surnames or proper nouns."

Score (word repetitions or variations [shoe, shoemaker], surnames, or proper nouns are not counted as correct responses)

> 9 words: 3 6 -9 words: 2 3 -5 words: 1 < 3 words: 0

3. Motor series "Luria" test (programming)

"Look carefully at what I'm doing."

The examiner, seated in front of the patient, performs alone three times with his left hand the series of "fist–edge–palm."

"Now, with your right hand do the same series, first with me, then alone."

The examiner performs the series three times with the patient, then says to him/her:

"Now, do it on your own."

Score

Patient performs six correct consecutive series alone: 3
Patient performs at least three correct consecutive series alone: 2

Patient fails alone, but performs three correct consecutive series with the examiner: 1

Patient cannot perform three correct consecutive series even with the examiner: 0

4. Conflicting instructions (sensitivity to interference)

"Tap twice when I tap once."

To ensure that the patient has understood the instruction, a series of 3 trials is run: 1-1-1. “Tap once when I tap twice.” To ensure that the patient has understood the instruction, a series of 3 trials is run: 2-2-2.

The examiner then performs the following series: 1-1-2-1-2-2-2-1-1-2.

Score No errors: 3 1 -2 errors: 2 > 2 errors: 1

Patient taps like the examiner at least four consecutive times: 0

5. Go–No Go (inhibitory control)

“Tap once when I tap once.” To ensure that the patient has understood the instruction, a series of 3 trials is run: 1-1-1.

“Do not tap when I tap twice.” To ensure that the patient has understood the instruction, a series of 3 trials is run: 2-2-2.

The examiner then performs the following series: 1-1-2-1-2-2-2-1-1-2.

Score No errors: 3 1 -2 errors: 2 > 2 errors: 1

Patient taps like the examiner at least four consecutive times: 0

6. Prehension behaviour (environmental autonomy)

“Do not take my hands.”

The examiner is seated in front of the patient. Place the patient’s hands palm up on his knees. Without saying anything or looking at the patient, the examiner brings his own hands close to the patient’s hands and touches the palms of both the patient’s hands, to see if he will spontaneously take them. If the patient takes the examiner’s hands, try again after asking the patient: “Now, do not take my hands.”

Score

Patient does not take the examiner’s hands: 3

Patient hesitates and asks what he/she has to do: 2

Patient takes the hands without hesitation: 1

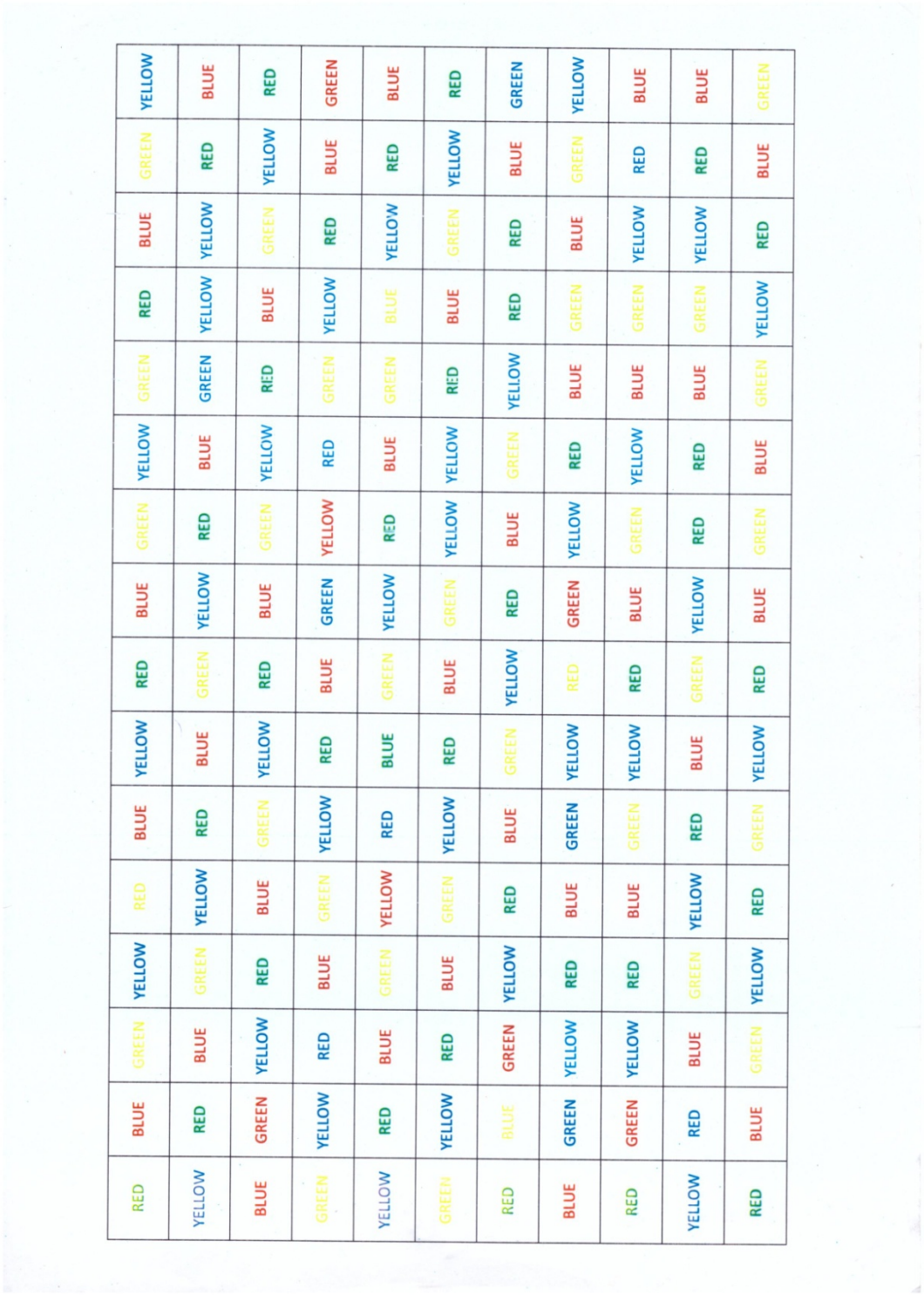
Patient takes the examiner’s hand even after he has been told not to do so: 0

Interpreting results

A cut off score of 12 on the FAB has a sensitivity of 77% and specificity of 87% in differentiating between frontal dysexecutive type dementias and DAT

ANNEXURE

STROOP TEST



STROOP TEST

பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்
நீலம்	பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு	மஞ்சள்
மஞ்சள்	நீலம்	பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு
சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை
மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்
நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்	பச்சை	மஞ்சள்	சிவப்பு
சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை
மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்
நீலம்	சிவப்பு	மஞ்சள்	பச்சை	நீலம்	சிவப்பு	மஞ்சள்	பச்சை	நீலம்	சிவப்பு	மஞ்சள்	பச்சை	நீலம்	சிவப்பு	மஞ்சள்	பச்சை	நீலம்	சிவப்பு	மஞ்சள்	பச்சை
சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை
பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்

NORMATIVE DATA –STROOP TEST

Table 15.2 Stroop Test – Literate Females – Sample Characteristics for each age x education category

Females												
	16-30 years				31-50 years				51-65 years			
	School educated		College educated		School educated		College educated		School educated		College educated	
N	32		30		30		30		26		36	
	Age	Edn.	Age	Edn.	Age	Edn.	Age	Edn.	Age	Edn.	Age	Edn.
Mean	22.09	9.03	24.00	16.57	40.27	8.23	39.00	15.43	55.65	7.96	55.26	14.51
SD	4.69	1.47	3.32	2.76	4.86	2.03	6.53	2.33	4.11	2.47	5.01	2.03
Note: Edn.=Education												

Table 15.3 Stroop Test – Literate Males – Stroop Effect Mean, S.D., Percentiles for each age x education category

Males												
	16-30 years				31-50 years				51-65 years			
	School educated		College educated		School educated		College educated		School educated		College educated	
N	34		31		31		33		30		35	
Mean SE	160.71		151.16		156.26		149.82		184.60		183.10	
SD	76.44		46.65		85.64		49.26		107.57		82.51	
	SE	Percentiles	SE	Percentiles	SE	Percentiles	SE	Percentiles	SE	Percentiles	SE	Percentiles
	381	3	288	3	434	3	261	3	536	3	368	3
	346	6	214	7	352	7	250	6	405	6	350	7
	295	9	213	10	267	10	215	9	402	9	333	10
	229	15	211	13	264	13	199	12	397	11	320	13
	215	18	210	16	257	16	196	15	283	14	274	17
	200	21	200	19	209	19	193	18	254	17	252	20
	197	24	181	23	199	23	192	21	240	20	244	23
	195	27	178	26	192	26	186	24	238	23	242	27
	192	29	176	29	173	29	185	27	215	26	233	30
	188	32	172	32	161	32	169	30	209	29	205	33

Table Contd..

NORMATIVE DATA –STROOP TEST

Males												
16-30 years				31-50 years				51-65 years				
School educated		College educated		School educated		College educated		School educated		College educated		
SE	Percentiles	SE	Percentiles	SE	Percentiles	SE	Percentiles	SE	Percentiles	SE	Percentiles	
178	35	167	36	156	36	163	33	202	31	181	37	
170	38	164	39	150	39	161	36	196	34	172	43	
162	41	163	42	145	42	155	39	189	37	161	47	
160	47	149	45	141	45	154	42	185	40	160	50	
158	50	148	48	136	52	152	46	182	43	159	53	
151	53	138	52	135	55	150	49	167	46	151	57	
144	56	135	55	132	58	149	52	145	49	147	60	
138	59	133	58	130	61	148	58	140	51	146	63	
135	62	131	65	125	65	147	61	138	54	143	67	
134	65	130	68	120	68	138	67	136	57	139	70	
133	68	126	71	111	71	136	70	135	60	135	73	
131	71	125	74	102	74	128	73	130	63	130	77	
124	74	124	77	101	77	126	76	126	66	128	80	
123	77	121	81	92	81	124	79	125	69	114	83	
114	79	112	84	90	84	120	82	121	71	112	87	
108	82	100	90	88	87	107	85	120	74	95	90	
98	85	85	94	85	90	87	88	118	77	93	93	
77	88	82	97	78	94	86	91	113	80	90	97	
73	91	79	100	55	97	84	94	108	83	44	100	
55	94			28	100	78	97	106	86			
54	97					19	100	98	91			
17	100							75	94			
								70	97			
								59	100			

Note: SE = Stroop Effect

Digit span test

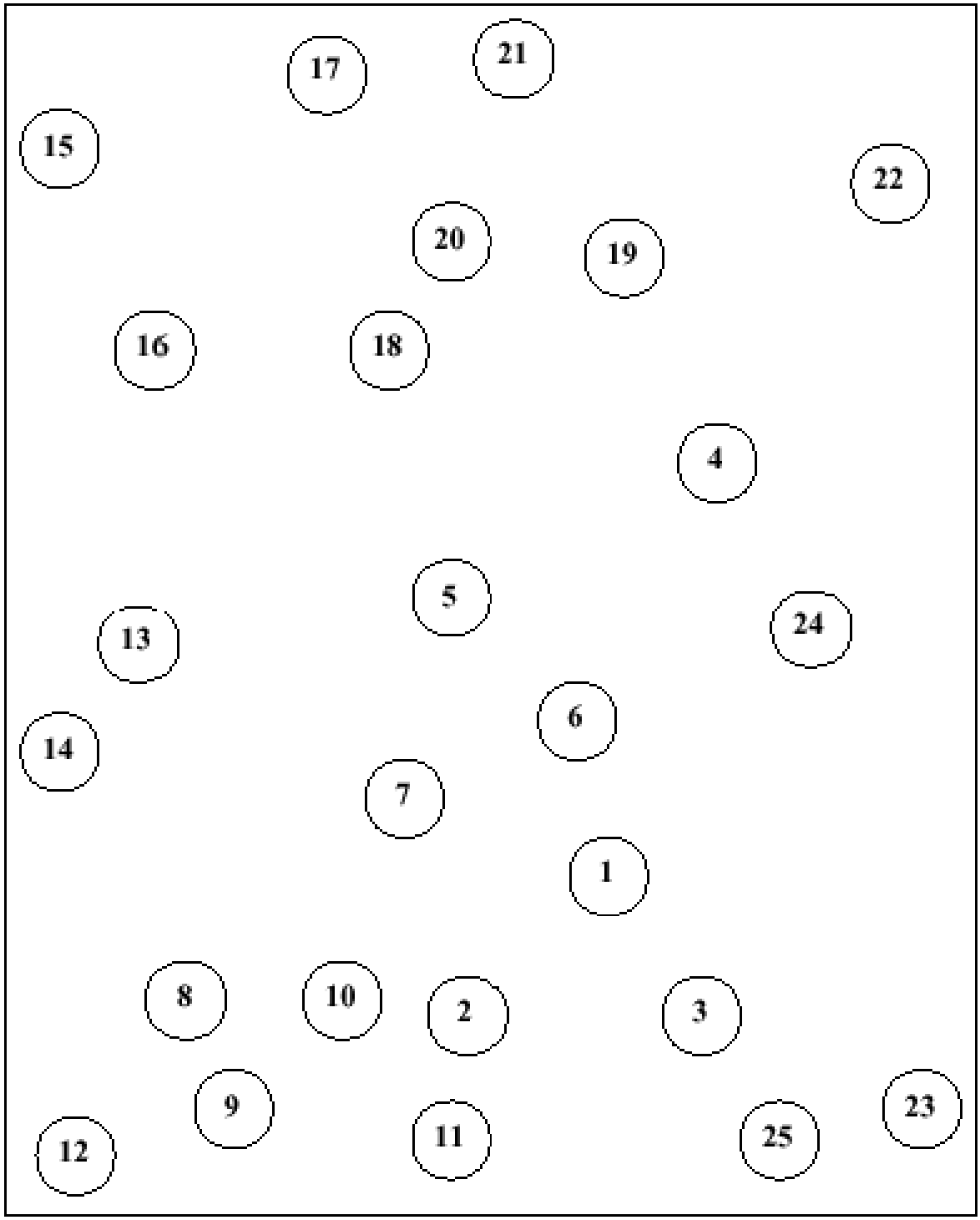
	Column 1	Column 2
Forward test	(3) 2−6-5 (4) 1−5−2-3 (5) 2−4−7−6-1 (6) 4-2−1−9−3−7 (7) 3−6−4−8−5−2-9 (8) 7−5−8−2−9−6−1-3 (9) 5−8−6−4−2−7−3−9-1	(3) 2−8-1 (4) 1−9−5-2 (5) 5−2−1−4-3 (6) 8−5−3−1−4-7 (7) 6−8−1−4−7−2-5 (8) 2−8-5-9−7−3−1-4 (9) 4−2−5−8−1−3−9−7-6
Backward test	(2) 2-1 (3) 5−8-4 (4) 4−8−9-1 (5) 6−8−7-2-1 (6) 5−8-1-7−4-6 (7) 8−5−3−6−7−2-9 (8) 1−7−4−3−8−9−5-2	(2) 2-8 (3) 3-2−8 (4) 2−9−4-1 (5) 3−5−9−7-6 (6) 4-3−1−9−2−5 (7) 5−3−2−4−1−6-8 (8) 6−8−4−7−5−3−9-2

Maximal digit number for forward test ( ) +

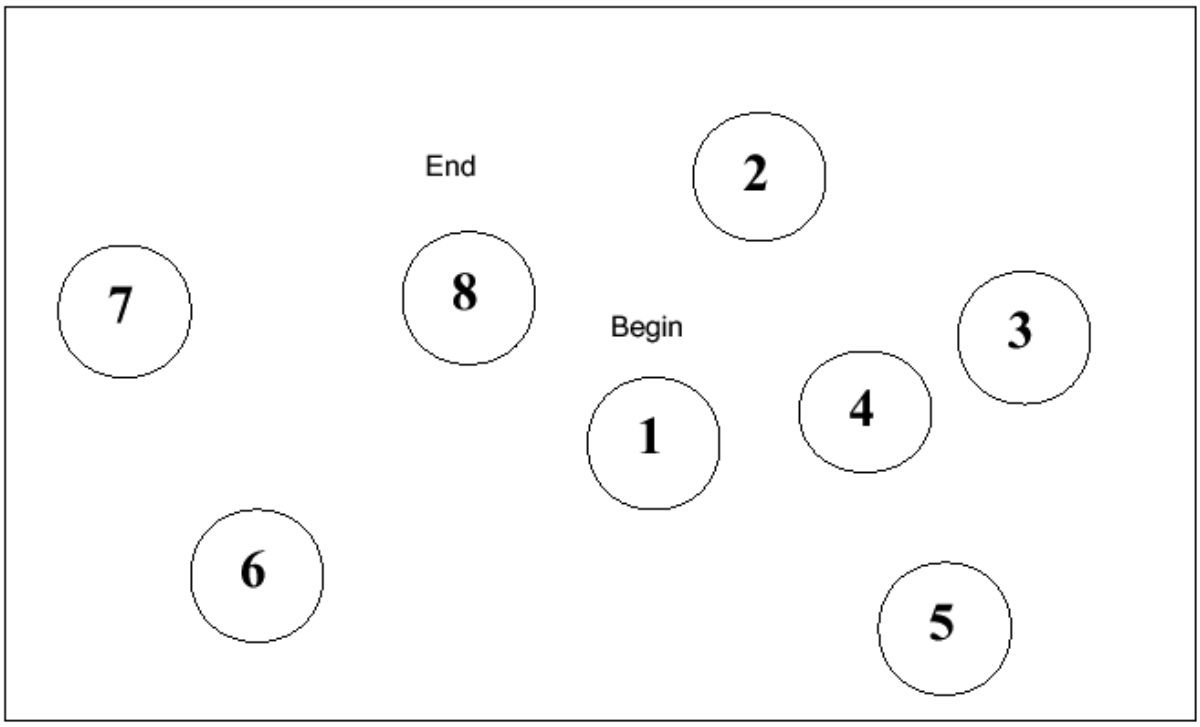
Maximal digit number for backward test ( ) = Total score ( )

Trail Making (Part A)

Patient's Name: _____ Date: _____

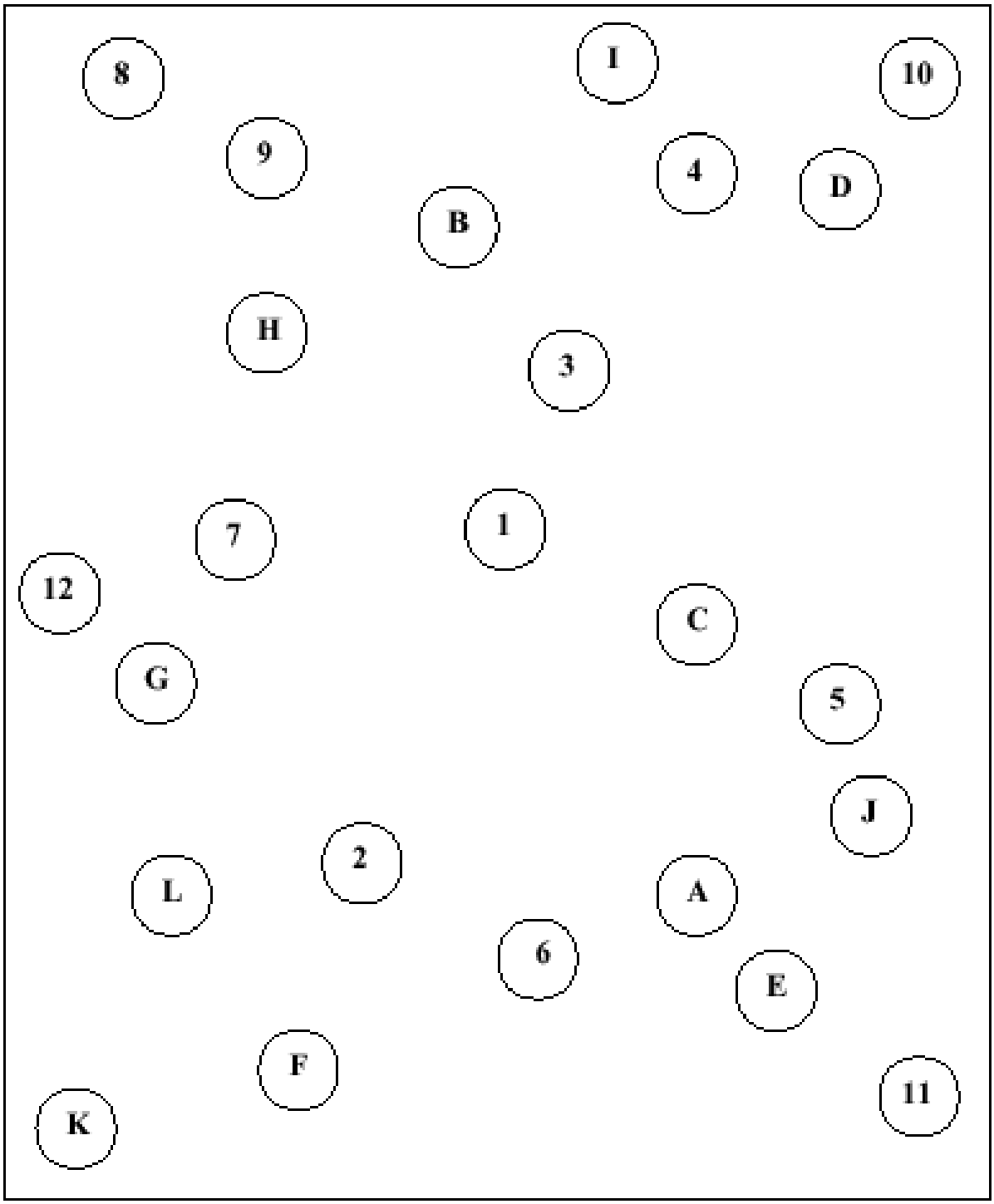


Trail Making (Part A) – *SAMPLE*

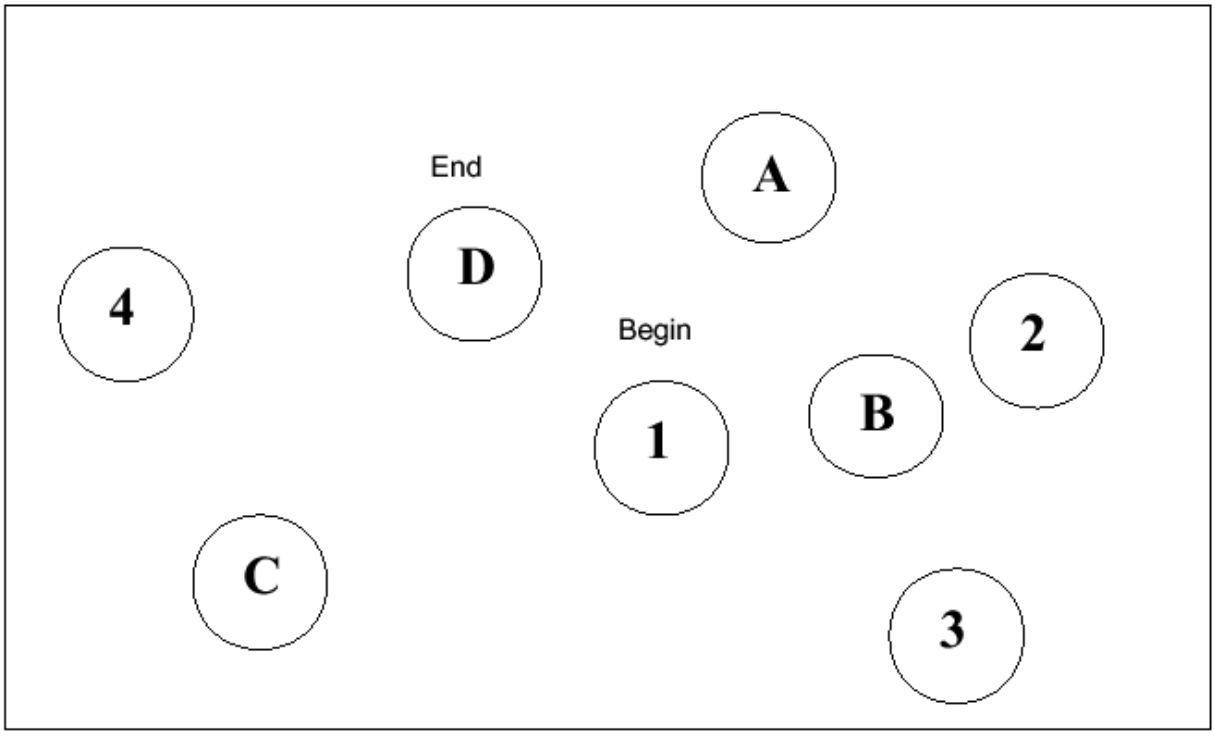


Trail Making (Part B)

Patient's Name: _____ Date: _____



Trail Making (Part B) – *SAMPLE*



Instructions:

Step 1: Give the patient a copy of the Trail Making Test (Part A) worksheet and a pen or pencil.

Step 2: Demonstrate the test to the patient using the sample sheet (Trail Making (Part A) – *SAMPLE*).

Step 3: Time the patient, as he or she follows the "trail" made by the numbers on the test.

Step 4: Record the time.

Step 5: Repeat for Trail Making Test (Part B).

Scoring:

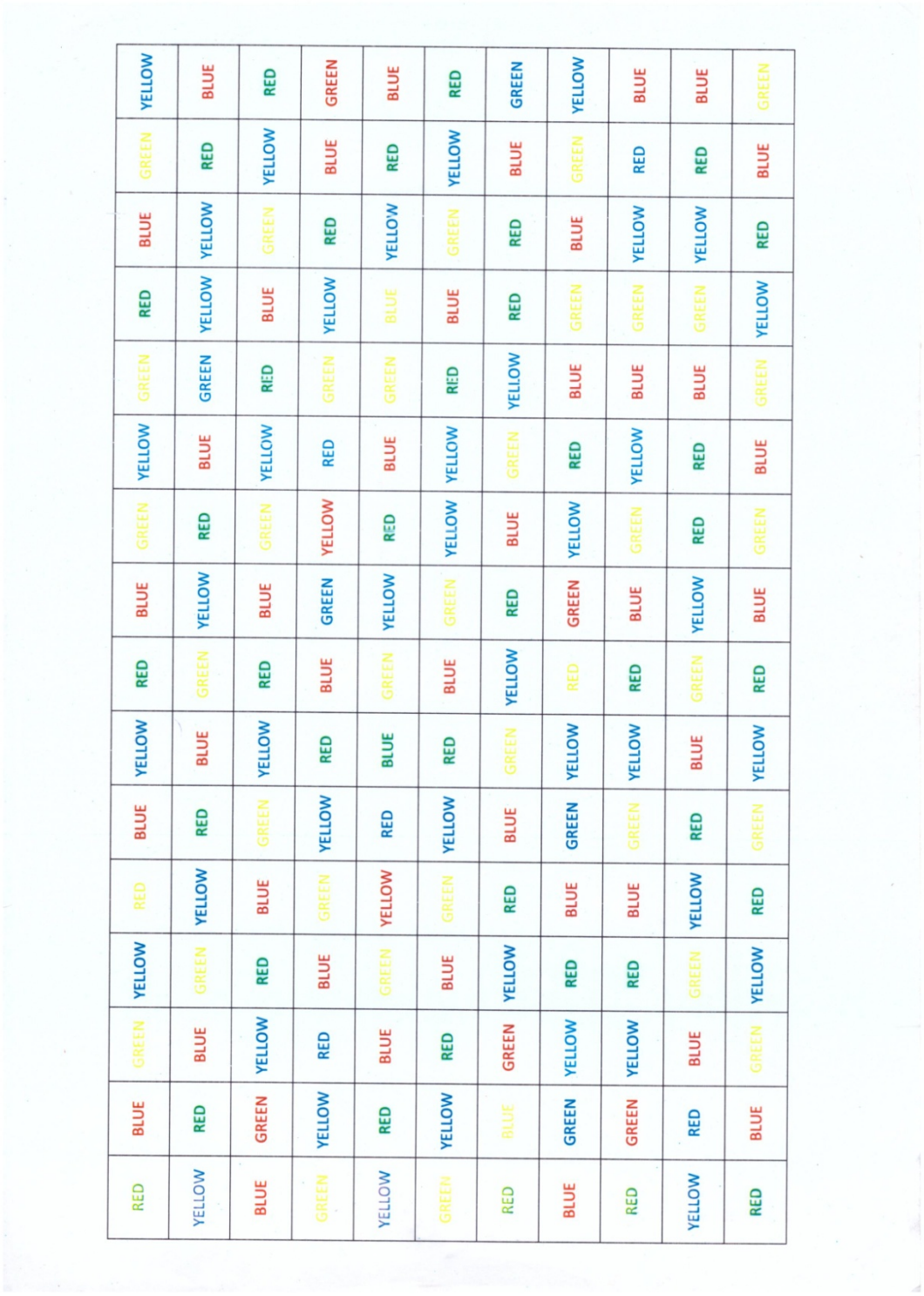
	Average	**Deficient**	**Rule of Thumb**
Trail A	29 seconds	> 78 seconds	Most in 90 seconds
Trail B	75 seconds	> 273	Most in 3 minutes

Source:

- Reitan RM. Validity of the Trail Making test as an indicator of organic brain damage. Percept Motor Skills 1958; 8: 271-276.
- Lezak MD (1995) Neuropsychological assessment, 3rd edn. New York: Oxford University Press.
- Corrigan JD, Hinkeldey MS. Relationships between Parts A and B of the Trail Making Test. J Clin Psychol 1987;43:402–9.

ANNEXURE 8

STROOP TEST



STROOP TEST

பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்
நீலம்	பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு	மஞ்சள்
மஞ்சள்	நீலம்	பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு
சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை
மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்
நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்	பச்சை	மஞ்சள்	சிவப்பு
சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை
மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்
நீலம்	சிவப்பு	மஞ்சள்	பச்சை	நீலம்	சிவப்பு	மஞ்சள்	பச்சை	நீலம்	சிவப்பு	மஞ்சள்	பச்சை	நீலம்	சிவப்பு	மஞ்சள்	பச்சை	நீலம்	சிவப்பு	மஞ்சள்	பச்சை
சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை
பச்சை	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்

NORMATIVE DATA –STROOP TEST

Table 15.2 Stroop Test – Literate Females – Sample Characteristics for each age x education category

Females												
	16-30 years				31-50 years				51-65 years			
	School educated		College educated		School educated		College educated		School educated		College educated	
N	32		30		30		30		26		36	
	Age	Edn.	Age	Edn.	Age	Edn.	Age	Edn.	Age	Edn.	Age	Edn.
Mean	22.09	9.03	24.00	16.57	40.27	8.23	39.00	15.43	55.65	7.96	55.26	14.51
SD	4.69	1.47	3.32	2.76	4.86	2.03	6.53	2.33	4.11	2.47	5.01	2.03
Note: Edn.=Education												

Table 15.3 Stroop Test – Literate Males – Stroop Effect Mean, S.D., Percentiles for each age x education category

Males												
	16-30 years				31-50 years				51-65 years			
	School educated		College educated		School educated		College educated		School educated		College educated	
N	34		31		31		33		30		35	
Mean SE	160.71		151.16		156.26		149.82		184.60		183.10	
SD	76.44		46.65		85.64		49.26		107.57		82.51	
	SE	Percentiles	SE	Percentiles	SE	Percentiles	SE	Percentiles	SE	Percentiles	SE	Percentiles
	381	3	288	3	434	3	261	3	536	3	368	3
	346	6	214	7	352	7	250	6	405	6	350	7
	295	9	213	10	267	10	215	9	402	9	333	10
	229	15	211	13	264	13	199	12	397	11	320	13
	215	18	210	16	257	16	196	15	283	14	274	17
	200	21	200	19	209	19	193	18	254	17	252	20
	197	24	181	23	199	23	192	21	240	20	244	23
	195	27	178	26	192	26	186	24	238	23	242	27
	192	29	176	29	173	29	185	27	215	26	233	30
	188	32	172	32	161	32	169	30	209	29	205	33

Table Contd..

NORMATIVE DATA –STROOP TEST

Males												
16-30 years				31-50 years				51-65 years				
School educated		College educated		School educated		College educated		School educated		College educated		
SE	Percentiles	SE	Percentiles	SE	Percentiles	SE	Percentiles	SE	Percentiles	SE	Percentiles	
178	35	167	36	156	36	163	33	202	31	181	37	
170	38	164	39	150	39	161	36	196	34	172	43	
162	41	163	42	145	42	155	39	189	37	161	47	
160	47	149	45	141	45	154	42	185	40	160	50	
158	50	148	48	136	52	152	46	182	43	159	53	
151	53	138	52	135	55	150	49	167	46	151	57	
144	56	135	55	132	58	149	52	145	49	147	60	
138	59	133	58	130	61	148	58	140	51	146	63	
135	62	131	65	125	65	147	61	138	54	143	67	
134	65	130	68	120	68	138	67	136	57	139	70	
133	68	126	71	111	71	136	70	135	60	135	73	
131	71	125	74	102	74	128	73	130	63	130	77	
124	74	124	77	101	77	126	76	126	66	128	80	
123	77	121	81	92	81	124	79	125	69	114	83	
114	79	112	84	90	84	120	82	121	71	112	87	
108	82	100	90	88	87	107	85	120	74	95	90	
98	85	85	94	85	90	87	88	118	77	93	93	
77	88	82	97	78	94	86	91	113	80	90	97	
73	91	79	100	55	97	84	94	108	83	44	100	
55	94			28	100	78	97	106	86			
54	97					19	100	98	91			
17	100							75	94			
								70	97			
								59	100			

Note: SE = Stroop Effect

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Young Mania Rating Scale (YMRS)

OVERVIEW

The Young Mania Rating Scale (YMRS) is one of the most frequently utilized rating scales to assess manic symptoms. The scale has 11 items and is based on the patient's subjective report of his or her clinical condition over the previous 48 hours. Additional information is based upon clinical observations made during the course of the clinical interview. The items are selected based upon published descriptions of the core symptoms of mania. The YMRS follows the style of the Hamilton Rating Scale for Depression (HAM-D) with each item given a severity rating. There are four items that are graded on a 0 to 8 scale (irritability, speech, thought content, and disruptive/aggressive behavior), while the remaining seven items are graded on a 0 to 4 scale. These four items are given twice the weight of the others to compensate for poor cooperation from severely ill patients. There are well described anchor points for each grade of severity. The authors encourage the use of whole or half point ratings once experience with the scale is acquired. Typical YMRS baseline scores can vary a lot. They depend on the patients' clinical features such as mania (YMRS = 12), depression (YMRS = 3), or euthymia (YMRS = 2). Sometimes a clinical study entry requirement of YMRS $\geq$ 20 generates a mean YMRS baseline of about 30. Strengths of the YMRS include its brevity, widely accepted use, and ease of administration. The usefulness of the scale is limited in populations with diagnoses other than mania.

The YMRS is a rating scale used to evaluate manic symptoms at baseline and over time in individuals with mania.

The scale is generally done by a clinician or other trained rater with expertise with manic patients and takes 15–30 minutes to complete.

REFERENCES

Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry.* 1978;133:429-435.

McIntyre RS, Mancini DA, Srinivasan J, McCann S, Konarski JZ, Kennedy SH. The antidepressant effects of risperidone and olanzapine in bipolar disorder. *Can J Clin Pharmacol.* 2004;11:e218-226.

Young RC, Biggs JT, Ziegler VE, Meyer DA. Young Mania Rating Scale. In: *Handbook of Psychiatric Measures*. Washington, DC: American Psychiatric Association; 2000:540-542.

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Young Mania Rating Scale (YMRS)

GUIDE FOR SCORING ITEMS:

The purpose of each item is to rate the severity of that abnormality in the patient. When several keys are given for a particular grade of severity, the presence of only one is required to qualify for that rating.

The keys provided are guides. One can ignore the keys if that is necessary to indicate severity, although this should be the exception rather than the rule.

Scoring between the points given (whole or half points) is possible and encouraged after experience with the scale is acquired. This is particularly useful when severity of a particular item in a patient does not follow the progression indicated by the keys.

1. **Elevated Mood**
   - 0 Absent
   - 1 Mildly or possibly increased on questioning
   - 2 Definite subjective elevation; optimistic, self-confident; cheerful; appropriate to content
   - 3 Elevated; inappropriate to content; humorous
   - 4 Euphoric; inappropriate laughter; singing

2. **Increased Motor Activity-Energy**
   - 0 Absent
   - 1 Subjectively increased
   - 2 Animated; gestures increased
   - 3 Excessive energy; hyperactive at times; restless (can be calmed)
   - 4 Motor excitement; continuous hyperactivity (cannot be calmed)

3. **Sexual Interest**
   - 0 Normal; not increased
   - 1 Mildly or possibly increased
   - 2 Definite subjective increase on questioning
   - 3 Spontaneous sexual content; elaborates on sexual matters; hypersexual by self-report
   - 4 Overt sexual acts (toward patients, staff, or interviewer)

4. **Sleep**
   - 0 Reports no decrease in sleep
   - 1 Sleeping less than normal amount by up to one hour
   - 2 Sleeping less than normal by more than one hour
   - 3 Reports decreased need for sleep
   - 4 Denies need for sleep

5. **Irritability**
   - 0 Absent
   - 2 Subjectively increased
   - 4 Irritable at times during interview; recent episodes of anger or annoyance on ward
   - 6 Frequently irritable during interview; short, curt throughout
   - 8 Hostile, uncooperative; interview impossible

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Young Mania Rating Scale (YMRS)

6. Speech (Rate and Amount)
- 0 No increase
- 2 Feels talkative
- 4 Increased rate or amount at times, verbose at times
- 6 Push; consistently increased rate and amount; difficult to interrupt
- 8 Pressured; uninterruptible, continuous speech

7. Language-Thought Disorder
- 0 Absent
- 1 Circumstantial; mild distractibility; quick thoughts
- 2 Distractible, loses goal of thought; changes topics frequently; racing thoughts
- 3 Flight of ideas; tangentiality; difficult to follow; rhyming, echolalia
- 4 Incoherent; communication impossible

8. Content
- 0 Normal
- 2 Questionable plans, new interests
- 4 Special project(s); hyper-religious
- 6 Grandiose or paranoid ideas; ideas of reference
- 8 Delusions; hallucinations

9. Disruptive-Aggressive Behavior
- 0 Absent, cooperative
- 2 Sarcastic; loud at times, guarded
- 4 Demanding; threats on ward
- 6 Threatens interviewer; shouting; interview difficult
- 8 Assaultive; destructive; interview impossible

10. Appearance
- 0 Appropriate dress and grooming
- 1 Minimally unkempt
- 2 Poorly groomed; moderately disheveled; overdressed
- 3 Disheveled; partly clothed; garish make-up
- 4 Completely unkempt; decorated; bizarre garb

11. Insight
- 0 Present; admits illness; agrees with need for treatment
- 1 Possibly ill
- 2 Admits behavior change, but denies illness
- 3 Admits possible change in behavior, but denies illness
- 4 Denies any behavior change

THE HAMILTON RATING SCALE FOR DEPRESSION

(to be administered by a health care professional)

Patient's Name _____

Date of Assessment _____

To rate the severity of depression in patients who are already diagnosed as depressed, administer this questionnaire. The higher the score, the more severe the depression.

For each item, write the correct number on the line next to the item. (Only one response per item)

1. DEPRESSED MOOD (Sadness, hopeless, helpless, worthless)

_____
- **0=** Absent
- **1=** These feeling states indicated only on questioning
- **2=** These feeling states spontaneously reported verbally
- **3=** Communicates feeling states non-verbally—i.e., through facial expression, posture, voice, and tendency to weep
- **4=** Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication

2. FEELINGS OF GUILT

_____
- **0=** Absent
- **1=** Self reproach, feels he has let people down
- **2=** Ideas of guilt or rumination over past errors or sinful deeds
- **3=** Present illness is a punishment. Delusions of guilt
- **4=** Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. SUICIDE

_____
- **0=** Absent
- **1=** Feels life is not worth living
- **2=** Wishes he were dead or any thoughts of possible death to self
- **3=** Suicidal ideas or gesture
- **4=** Attempts at suicide (any serious attempt rates 4)

4. INSOMNIA EARLY

_____
- **0=** No difficulty falling asleep
- **1=** Complains of occasional difficulty falling asleep—i.e., more than 1/2 hour
- **2=** Complains of nightly difficulty falling asleep

5. INSOMNIA MIDDLE

_____
- **0=** No difficulty
- **1=** Patient complains of being restless and disturbed during the night
- **2=** Waking during the night—any getting out of bed rates 2 (except for purposes of voiding)

Adapted from Hedlung and Vieweg, The Hamilton rating scale for depression, *Journal of Operational Psychiatry*, 1979;10(2):149-165.

6. **INSOMNIA LATE**

_____ **0=** No difficulty
1= Waking in early hours of the morning but goes back to sleep
2= Unable to fall asleep again if he gets out of bed

7. **WORK AND ACTIVITIES**

_____ **0=** No difficulty
1= Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
2= Loss of interest in activity; hobbies or work—either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
3= Decrease in actual time spent in activities or decrease in productivity
4= Stopped working because of present illness

8. **RETARDATION: PSYCHOMOTOR** (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)

_____ **0=** Normal speech and thought
1= Slight retardation at interview
2= Obvious retardation at interview
3= Interview difficult
4= Complete stupor

9. **AGITATION**

_____ **0=** None
1= Fidgetiness
2= Playing with hands, hair, etc.
3= Moving about, can't sit still
4= Hand wringing, nail biting, hair-pulling, biting of lips

10. **ANXIETY (PSYCHOLOGICAL)**

_____ **0=** No difficulty
1= Subjective tension and irritability
2= Worrying about minor matters
3= Apprehensive attitude apparent in face or speech
4= Fears expressed without questioning

11. **ANXIETY SOMATIC:** Physiological concomitants of anxiety, (i.e., effects of autonomic overactivity, "butterflies," indigestion, stomach cramps, belching, diarrhea, palpitations, hyperventilation, paresthesia, sweating, flushing, tremor, headache, urinary frequency). Avoid asking about possible medication side effects (i.e., dry mouth, constipation)

_____ **0=** Absent
1= Mild
2= Moderate
3= Severe
4= Incapacitating

12. SOMATIC SYMPTOMS (GASTROINTESTINAL)

_____ **0**= None
1= Loss of appetite but eating without encouragement from others. Food intake about normal
2= Difficulty eating without urging from others. Marked reduction of appetite and food intake

13. SOMATIC SYMPTOMS GENERAL

_____ **0**= None
1= Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability
2= Any clear-cut symptom rates 2

14. GENITAL SYMPTOMS (Symptoms such as: loss of libido; impaired sexual performance; menstrual disturbances)

_____ **0**= Absent
1= Mild
2= Severe

15. HYPOCHONDRIASIS

_____ **0**= Not present
1= Self-absorption (bodily)
2= Preoccupation with health
3= Frequent complaints, requests for help, etc.
4= Hypochondriacal delusions

16. LOSS OF WEIGHT

_____ **A.** When rating by history:
0= No weight loss
1= Probably weight loss associated with present illness
2= Definite (according to patient) weight loss
3= Not assessed

17. INSIGHT

_____ **0**= Acknowledges being depressed and ill
1= Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2= Denies being ill at all

18. DIURNAL VARIATION

_____ **A.** Note whether symptoms are worse in morning or evening. If NO diurnal variation, mark none
0= No variation
1= Worse in A.M.
2= Worse in P.M.

_____ **B.** When present, mark the severity of the variation. Mark "None" if NO variation
0= None
1= Mild
2= Severe

19. DEPERSONALIZATION AND DEREALIZATION (Such as: Feelings of unreality; Nihilistic ideas)

_____ **0**= Absent
1= Mild
2= Moderate
3= Severe
4= Incapacitating

20. PARANOID SYMPTOMS

_____ **0**= None
1= Suspicious
2= Ideas of reference
3= Delusions of reference and persecution

21. OBSESSIONAL AND COMPULSIVE SYMPTOMS

_____ **0**= Absent
1= Mild
2= Severe

Total Score _____

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GlaxoWellcome

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Research Triangle Park, NC 27709
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Printed in USA. WEL056R0 February 1997

S No	name	age	sex	marital st	education	occupation	duration of illness	episodes no.	treatment	duration of treatment(years)	no.of manic episodes	no of depressive episodes	gaf	WHOQOL-BREFphysiological	psychological	social	environmental		DF	DB		stroop test-B		FAB score	FAB-similarities	FAB-lexical fluency	FAB-motor luria	FAB-conflicting instructiond	FAB-go no go	FAB-prehension		TMT-A:time(secs)	TMT-B:time(secs)
1	premkuma	29	M	s	ix	machinist	7	6	svp-1200mg; li-600mg	5	2	0	8	75	69	63	81		5	4		312		13	3	2	1	2	2	3		71	312
2	muneer m	37	M	s	x	waiter	9	3	svp-1200mg;li-900mg	1	0	0	9	69	81	75	63		5	4		309		18	3	3	3	3	3	3		56	295
3	sarala	42	F	m	iv	housewife	8	3	svp-800mg,li-600mg	3	0	0	9	88	81	69	75		5	4		267		16	3	2	2	3	3	3		49	290
4	yamuna	33	F	m	dipco	salesperso	7	2	svp-600mg;li-600mg	4	0	0	10	94	88	75	81		6	6		252		18	3	3	3	3	3	3		32	256
5	velu	45	M	m	v	watchman	15	7	svp-1200mg; li-600mg	7	1	1	8	75	56	69	56		3	2		331		12	2	2	2	3	3	3		84	308
6	ezhilarasi	48	F	m	mca	housewife	9	2	svp-800mg;li-900mg	7	0	0	10	94	81	94	88		6	5		255		18	3	3	3	3	3	3		35	252
7	samuel	44	M	m	iti	watchman	24	9	svp-1200mg;li-1200mg	13	3	0	8	50	44	56	63		2	2		376		10	2	1	1	2	2	2		90	321
8	priya	41	F	sep	xi	housewife	13	5	svp-1200mg;li-900mg	6	2	0	8	69	56	75	63		3	cant do		342		9	1	1	1	2	2	2		85	302
9	dattathrey	36	M	m	viii	watchman	12	3	svp-800mg,li-1200mg	8	0	0	9	75	69	81	81		3	2		290		11	2	2	1	2	2	2		38	269
10	sunderraj	22	M	s	xii	salesperso	2	1	svp-1200mg;li-600mg	2	1	0	10	81	94	81	88		5	5		247		18	3	3	3	3	3	3		41	248
11	leena	29	F	s	xii	salesperso	7	5	svp-1200mg, li-600mg	5	1	0	8	75	69	81	63		5	4		303		16	3	2	2	3	3	3		57	279
12	naveen	39	M	m	ix	machinist	5	1	svp-800mg;li-900mg	5	1	0	9	81	75	94	81		5	4		252		15	3	2	1	3	3	3		39	245
13	sounder	33	M	s	iti	welder	8	2	svp-1200mg;li-900mg	8	1	1	8	69	56	69	63		4	2		249		12	3	2	1	2	2	2		44	259
14	gokulan	50	M	wr	v	watchman	26	15	svp-1200mg;li-1800mg	19	3	2	6	50	31	44	38		2	2		398		8	2	2	0	0	2	2		94	353
15	thinagaran	38	M	m	v	coolie	13	3	svp-600mg;li-1200mg	13	2	1	8	75	75	81	69		3	2		288		11	2	1	2	1	2	2		36	264
16	emanuel	29	M	m	x	shopkeepe	4	2	svp-800mg;li-900mg	1	0	0	10	88	94	88	100		6	6		238		18	3	3	3	3	3	3		40	255
17	rathnavel	53	M	m	vii	watchman	18	7	svp-1200mg;li-1200mg	10	2	0	5	44	31	44	56		2	cant do		306		8	2	2	0	1	1	2		77	293
18	sagayam	42	M	m	x	watchman	7	4	svp-1200mg;li-900mg	3	0	0	8	75	81	69	88		5	4		317		15	3	3	2	2	2	3		79	276
19	paramesw	52	F	w	vi	housewife	20	13	svp-1200mg;li-900mh	5	2	0	7	56	63	75	75		4	3		333		14	3	2	2	2	2	3		97	333
20	devaki	47	F	m	v	housewife	23	9	svp-1000mg;li-600mg	10	2	0	7	63	56	69	75		3	2		319		13	3	2	1	2	2	3		71	295
21	renuka	25	F	s	xii	shopkeepe	3	2	svp-800mg;li-600mg	2	0	0	10	88	94	94	100		6	6		238		18	3	3	3	3	3	3		58	253
22	celina	20	F	s	xii	unemploye	2	2	svp-400mg;li-900mg	1.5	0	0	10	94	94	100	88		6	5		229		17	3	3	2	3	3	3		47	248
23	valli	39	F	m	iv	housewife	15	8	svp-1200mg;li-1200mg	4	1	0	8	69	75	81	63		4	3		311		15	2	3	2	3	3	2		83	272
24	kanniamm	49	F	m	vii	housewife	22	15	svp-1200mg;li-1500mg	6	2	1	6	63	56	56	63		2	cant do		372		10	2	1	1	2	2	2		92	306
25	hussein	24	M	s	iti	mechanic	3	2	svp-600mg;li-900mg	2	0	0	10	88	94	100	94		6	6		245		18	3	3	3	3	3	3		36	257

26	kumaragur	36	M	s	viii	officeboy	16	8	svp-1200mg;li-1200mg	2	1	0	7	75	69	75	63		6	3		295		16	2	3	2	3	3	3		86	287
27	rasheed	23	M	s	vi	unemploye	4	3	svp-600mg;li-1200mg	3	0	0	8	75	69	50	56		4	4		266		15	2	2	2	3	3	3		35	257
28	mohanraj	48	M	m	v	machinist	11	6	svp-1200mg;li-900mg	7	1	0	7	69	75	69	81		4	3		294		14	2	2	2	3	3	2		60	268
29	jamuna	44	F	sep	x	cook	8	4	svp-800mg;li-1200mg	4	0	0	8	81	88	81	75		5	4		258		15	2	2	2	3	3	3		44	261
30	gomathy	26	F	m	vi	housemaid	2	2	svp-600mg;li-900mg	1	0	0	10	94	100	100	100		6	6		217		18	3	3	3	3	3	3		39	247
31	daniel	44	M	m	bsc cs	entreprene	9	9	svp-800mg;li-1200mg	3	1	0	7	75	69	81	81		5	5		298		16	2	2	3	3	3	3		22	267
32	charumath	21	F	s	xii	unemploye	1	1	svp-400mg;li-600mg	1	0	0	9	94	100	94	100		7	6		189		18	3	3	3	3	3	3		30	243
33	poovarasa	22	M	s	iti	welder	2	1	svp-600mg;li-600mg	2	0	0	8	88	100	94	94		6	5		209		18	3	3	3	3	3	3		33	250
34	anitha	38	F	m	xii	housewife	6	2	svp-600mg;li-600mg	4	0	0	7	94	88	94	81		5	5		228		18	3	3	3	3	3	3		29	253
35	haseena	32	F	m	iv	housewife	4	4	svp-800mg;li-900mg	2	0	0	8	94	88	81	81		4	3		273		17	3	2	3	3	3	3		37	259
36	rahman	30	M	m	viii	waiter	4	2	svp-800mg;li-600mg	2.5	0	0	8	88	81	94	88		4	4		234		16	3	2	2	3	3	3		31	249
37	thaarani	27	F	m	xii	housewife	2	1	svp-600mg;li-900mg	2	0	0	8	94	88	94	88		6	4		197		17	3	3	2	3	3	3		28	245
38	gopi	45	M	sep	x	peon	12	10	svp-1200mg;li-1500mg	8	2	2	6	56	50	44	44		2	cant do		319		9	1	2	1	2	1	2		82	271
39	kokila	33	F	m	ix	housewife	5	3	svp-1000mg;li-600mg	1	0	0	8	81	81	81	94		5	4		231		17	3	3	2	3	3	3		51	252
40	kadar khar	52	M	sep	iv	watchman	30	9	svp-1200mg;li-1500mg	24	4	2	5	50	38	44	25		3	2		284		10	2	1	1	2	2	2		95	277
1	munirathn	52	M	m	xii	watchman	9	3	svp-400mg	9	2	0	7	56	44	75	69		5	5		274		15	3	2	2	2	3	3		34	258
2	govindasar	54	M	wr	ix	watchman	28	12	svp-1200mg	28	4	7	5	25	38	50	44		4	3		344		10	2	1	1	2	2	2		59	313
3	abdul kade	49	M	m	viii	watchman	11	6	svp-1200mg	11	5	0	6	38	44	56	50		3	3		382		13	3	2	2	2	2	2		48	274
4	udhayaraj	29	M	s	x	officeboy	5	4	svp-1000mg	5	2	1	6	38	50	44	31		5	5		369		17	3	3	2	3	3	3		45	263
5	ramamoor	53	M	sep	iv	coolie	10	3	svp-1000mg	9	2	0	6	50	38	56	44		2	cant do		279		9	2	2	0	1	2	2		36	259
6	babu	38	M	m	viii	mechanic	20	9	svp-800mg	20	5	3	6	31	38	69	50		3	2		297		12	3	2	1	1	2	3		53	285
7	fareeda	32	F	m	xi	housewife	8	3	svp-800mg	8	3	0	6	44	38	31	50		4	3		212		15	3	3	1	3	2	3		46	261
8	clive	50	M	wr	x	watchman	22	7	svp-1200mg	20	6	2	5	31	44	25	38		4	4		306		16	3	3	2	3	2	3		58	319
9	harini	31	F	s	xii	salesperso	11	4	svp-1000mg	11	4	1	7	44	50	56	69		5	3		362		15	3	3	2	2	2	3		39	281
10	saranya	20	F	s	x	unemploye	3	2	svp-800mg	3	1	0	8	88	94	81	75		6	4		229		18	3	3	3	3	3	3		31	257
11	ramadevi	28	F	s	viii	unemploye	6	2	svp-800mg	6	2	0	8	56	56	69	75		6	4		243		17	3	3	2	3	3	3		32	263
12	shyamala	38	F	m	vi	housewife	6	2	svp-800mg	6	0	0	7	56	50	44	38		4	3		249		12	2	2	2	2	2	2		35	259
13	kumutha	42	F	m	v	housewife	14	3	svp-1200mg	12	1	0	6	50	63	69	56		5	4		251		16	3	2	2	3	3	3		41	265
14	tharani	31	F	s	ix	unemploye	4	2	svp-800mg	4	1	0	6	50	56	69	75		6	6		225		18	3	3	3	3	3	3		27	249
15	ponnamm	26	F	m	vii	housewife	3	1	svp-600mg	3	0	0	8	75	88	81	75		6	5		188		18	3	3	3	3	3	3		25	242
16	rajendran	28	M	m	vii	coolie	10	4	svp-1200mg	9	1	1	5	31	44	38	50		5	4		219		15	3	3	2	2	2	3		50	268
17	padmanab	33	M	m	vi	mechanic	8	3	svp-1200mg	8	2	0	6	44	56	38	50		6	6		273		18	3	3	3	3	3	3		38	265
18	edison	27	M	m	x	machinist	2	1	svp-600mg	2	0	0	9	81	69	75	94		6	6		192		18	3	3	3	3	3	3		26	243
19	pushpa	29	F	s	bsc m	teacher	3	1	svp-800mg	3	0	0	10	81	88	94	81		6	6		169		18	3	3	3	3	3	3		29	245

20	derina	37	F	m	vii	housewife	9	2	svp-1000mg	9	0	1	6	56	63	38	31		5	3		207		13	3	2	1	2	2	3		34	252
21	yousuf	45	M	m	iv	unemploye	8	3	svp-1000mg	8	1	2	6	38	44	25	31		4	2		219		16	3	2	2	3	3	3		37	259
22	samy	42	M	m	ix	watchman	7	8	svp-1200mg	6	4	3	5	44	38	56	50		4	3		241		15	3	2	2	3	3	2		72	284
23	kothandan	38	M	m	v	coolie	3	6	svp-1200mg	3	3	2	6	50	63	44	50		5	3		269		17	3	2	3	3	3	3		63	277
24	ravi	46	M	sep	viii	coolie	22	15	svp-1200mg	22	8	6	4	31	19	25	25		3	cant do		287		8	2	1	0	1	2	2		77	357
25	sajini	30	F	m	xii	housewife	5	2	svp-800mg	5	1	0	6	56	50	69	63		4	4		239		17	3	3	2	3	3	3		37	266
26	malliga	33	F	s	bcom	receptionis	8	6	svp-1000mg	7	2	2	6	63	44	69	63		6	5		298		18	3	3	3	3	3	3		73	284
27	vanitha	21	F	s	xi	salesperso	1	2	svp-800mg	1	1	0	9	69	81	75	88		5	4		267		18	3	3	3	3	3	3		38	253
28	babu.s	24	M	s	iti	mechanic	4	5	svp-1000mg	4	4	0	7	63	44	50	69		5	4		281		16	3	2	2	3	3	3		59	277
29	balaguru	29	M	m	x	mechanic	3	2	svp-800mg	3	1	0	7	56	50	69	63		4	3		263		18	3	3	3	3	3	3		36	253
30	krithika	20	F	s	xii	unemploye	1	1	svp-600mg	1	0	0	8	75	69	81	94		4	4		249		18	3	3	3	3	3	3		29	246
31	amsa	41	F	m	vi	housewife	7	7	svp-1200mg	7	4	2	6	56	44	69	75		4	3		318		10	2	2	1	1	1	3		20	294
32	rajam	50	F	w	iv	housewife	26	16	svp-1200mg	26	9	6	5	13	19	31	44		2	0		329		6	1	1	1	1	1	1		86	356
33	arulmozhi	38	F	m	vii	housewife	5	8	svp-1200mg	5	3	4	7	44	25	50	56		5	3		363		14	3	3	2	2	2	2		74	282
34	balakrishn	45	M	m	xi	machinist	23	10	svp-1200mg	21	6	2	6	25	38	44	50		2	0		349		8	2	1	1	1	1	2		90	323
35	padmavath	27	F	s	xii	housemaid	2	2	svp-600mg	2	1	0	8	63	63	75	69		6	5		233		17	3	3	2	3	3	3		30	253
36	leelavathy	47	F	m	v	housewife	18	9	svp-1000mg	18	3	5	6	31	31	50	56		4	2		337		9	2	2	1	1	1	2		59	287
37	rajkumar	54	M	m	x	unemploye	22	13	svp-1200mg	22	12	0	5	50	44	31	31		3	0		387		7	1	1	1	1	1	2		89	336
38	sarangapa	25	M	s	iti	welder	3	1	svp-400mg	3	0	0	8	75	75	81	88		5	5		210		18	3	3	3	3	3	3		28	243
39	geetha	34	F	m	vi	housewife	3	2	svp-600mg	3	1	0	8	69	69	75	63		5	5		216		16	3	3	2	3	2	3		35	251
40	balasubrar	40	M	m	vii	machinist	12	8	svp-1200mg	12	6	1	7	38	50	69	63		3	3		266		12	3	2	1	2	2	2		76	299